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Date: June 20, 2002



Arthur D. Dawson
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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Group No.: 1614

David R. Adams, et al.

Serial No.: 10/010,058

Filed: December 7, 2001

For: NOVEL PIPERAZINE DERIVATIVES

TRANSMITTAL OF CERTIFIED COPY

June 20, 2002

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

<u>Country</u>	<u>Application No.</u>	<u>Filing Date</u>
Great Britain	0030710.8	December 15, 2000

Respectfully submitted,

Arthur D. Dawson

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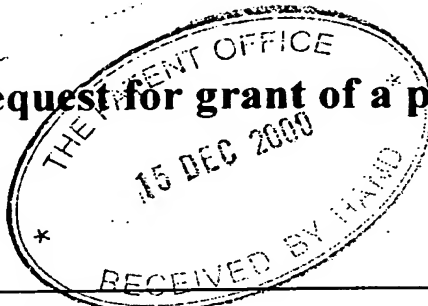
R. Mahoney

Signed

Dated 6 November 2001

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Request for grant of a patent



The Patent Office

Concept House
Cardiff Road
Newport
South Wales, NP10 8QQ

1.	Your reference	P14968GB-KR/GDP/gdp	
2.	Patent application number <i>(The Patent Office will fill in this part)</i>	0030710.8	
3.	Full name, address and postcode of the or of each applicant <i>(underline all surnames)</i>	F. Hoffmann-La Roche AG 124 Grenzacherstrasse CH-4070 Basle Switzerland Patents ADP number <i>(if you know it)</i> 7963051001 If the applicant is a corporate body, give the country/state of its incorporation SWITZERLAND	Vernalis Research Limited Oakdene Court 613 Reading Road Winnersh, Wokingham RG41 5UA United Kingdom 7915184001 UNITED KINGDOM
4.	Title of the invention	Piperazine Derivatives	
5.	Name of your agent <i>(if you have one)</i>	Forrester Ketley & Co.	
	"Address for service" in the United Kingdom to which all correspondence should be sent <i>(including the postcode)</i>	Forrester House 52 Bounds Green Road London N11 2EY Patents ADP number <i>(if you know it)</i> 133001	
6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and <i>(if you know it)</i> the or each application number	Country	Priority application number <i>(if you know it)</i> Date of filing <i>(day/month/year)</i>
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing <i>(day/month/year)</i>
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? <i>(Answer "Yes" if:</i> a) <i>any applicant named in part 3 is not an inventor, or</i> b) <i>there is an inventor who is not named as an applicant,</i> <i>or</i> c) <i>any named applicant is a corporate body.</i> <i>See note (d))</i>	YES	

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document.

Continuation sheets of this form	-
Description	49
Claim(s)	31
Abstract	1
Drawing(s)	-



10. If you are also filing any of the following, state how many against each item.

Priority documents	NONE
Translation of priority documents	-
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	-
Request for preliminary examination and search (Patents Form 9/77)	-
Request for substantive examination (Patents Form 10/77)	-
Any other documents (please specify)	-

11. I/We request the grant of a patent based on the basis of this application

Signature	Date
<i>Forrester Ketley & Co.</i>	15 December, 2000
Forrester Ketley & Co.	

12. Name and daytime telephone number of person to contact in the United Kingdom
- | | |
|-----------------|-----------------|
| Kate RICHARDSON | (020) 8889 6622 |
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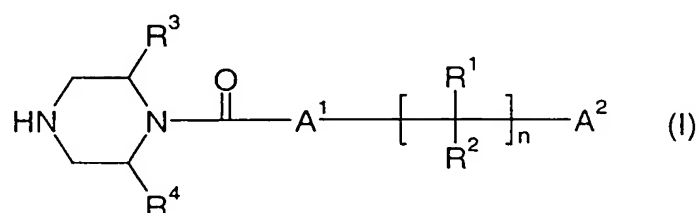
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Case 20791

Piperazine Derivatives

The present invention relates to new piperazine derivatives, to processes and intermediates for their preparation, to pharmaceutical compositions containing them and
5 to their medicinal use. The active compounds of the present invention are useful in treating obesity and other disorders.

The invention is concerned particularly with compounds of formula I and their pharmaceutically usable salts, solvates and esters



10 wherein

R¹ and R² are independently selected from hydrogen, alkyl, cycloalkyl, aryl and aralkyl or R¹ and R² together with the carbon atom to which they are attached form a 3- to 8-membered carbocyclic ring which is optionally substituted with alkyl;

R³ and R⁴ are independently selected from hydrogen, alkyl, cycloalkyl, aryl and aralkyl;

15 A¹ is oxygen or sulfur, wherein in case A¹ is oxygen and A² is unsubstituted phenyl one of R¹, R², R³ and R⁴ is not hydrogen;

A² is aryl, heteroaryl or cycloalkyl each optionally substituted with one or more substituents independently selected from halogen, alkyl, cycloalkyl, aryl, aralkyl, alkoxy, aralkoxy, aryloxy, hydroxy, cyano, nitro, amino, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heteroaryloxycarbonyl and carbamoyl, wherein alkyl, cycloalkyl, aryl, aralkyl, alkoxy, aralkoxy, aryloxy, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl and heteroaryloxycarbonyl are optionally substituted with one to three substituents independently selected from alkyl, alkoxy, halogen and nitro, or two substituents of aryl, heteroaryl or cycloalkyl form together with the carbon atoms to which they are attached a 5- to 7-membered carbocyclic ring which is optionally substituted with alkyl, alkoxy or halogen;

n is 1 or 2;

and, wherein 2-methyl-1-piperazinecarboxylic acid (4-nitophenyl)methyl ester and 1-piperazinecarboxylic acid (4-(trifluoromethyl)phenyl)methyl ester are excluded.

15

It has been recognised that obesity is a disease process influenced by environmental factors in which the traditional weight loss methods of dieting and exercise need to be supplemented by therapeutic products (S. Parker, "Obesity: Trends and Treatments", Scrip Reports, PJB Publications Ltd, 1996).

20

Whether someone is classified as overweight or obese is generally determined on the basis of their body mass index (BMI) which is calculated by dividing body weight (kg) by height squared (m²). Thus, the units of BMI are kg/m² and it is possible to calculate the BMI range associated with minimum mortality in each decade of life. Overweight is defined as a BMI in the range 25-30 kg/m², and obesity as a BMI greater than 30 kg/m². There are problems with this definition in that it does not take into account the proportion of body mass that is muscle in relation to fat (adipose tissue). To account for this, obesity can also be defined on the basis of body fat content: greater than 25% and 30% in males and females, respectively.

30

As the BMI increases there is an increased risk of death from a variety of causes that is independent of other risk factors. The most common diseases with obesity are cardiovascular disease (particularly hypertension), diabetes (obesity aggravates the

development of diabetes), gall bladder disease (particularly cancer) and diseases of reproduction. Research has shown that even a modest reduction in body weight can correspond to a significant reduction in the risk of developing coronary heart disease.

5 Compounds marketed as anti-obesity agents include Orlistat (XENICAL[®]) and Sibutramine. Orlistat (a lipase inhibitor) inhibits fat absorption directly and tends to produce a high incidence of unpleasant (though relatively harmless) side-effects such as diarrhoea. Sibutramine (a mixed 5-HT/noradrenaline reuptake inhibitor) can increase blood pressure and heart rate in some patients. The serotonin releaser/reuptake inhibitors
10 fenfluramine (Pondimin[®]) and dexfenfluramine (ReduxTM) have been reported to decrease food intake and body weight over a prolonged period (greater than 6 months). However, both products were withdrawn after reports of preliminary evidence of heart valve abnormalities associated with their use. There is therefore a need for the development of a safer anti-obesity agent.

15 The non-selective 5-HT_{2C} receptor agonists/partial agonists m-chlorophenylpiperazine (mCPP) and trifluoromethylphenylpiperazine (TFMPP) have been shown to reduce food intake in rats (G.A. Kennett and G. Curzon, *Psychopharmacol.*, 1988, 96, 93-100; G.A. Kennett, C.T. Dourish and G. Curzon, *Eur. J. Pharmacol.*, 1987, 141,
20 429-435) and to accelerate the appearance of the behavioural satiety sequence (S.J. Kitchener and C.T. Dourish, *Psychopharmacol.*, 1994, 113, 369-377). Recent findings from studies with mCPP in normal human volunteers and obese subjects have also shown decreases in food intake. Thus, a single dose of mCPP decreased food intake in female volunteers (A.E.S. Walsh *et al.*, *Psychopharmacol.*, 1994, 116, 120-122) and decreased the
25 appetite and body weight of obese male and female subjects during subchronic treatment for a 14 day period (P.A. Sargeant *et al.*, *Psychopharmacol.*, 1997, 133, 309-312). The anorectic action of mCPP is absent in 5-HT_{2C} receptor knockout mutant mice (L.H. Tecott *et al.*, *Nature*, 1995, 374, 542-546) and is antagonised by the 5-HT_{2C} receptor antagonist SB-242084 in rats (G.A. Kennett *et al.*, *Neuropharmacol.*, 1997, 36, 609-620). It
30 seems therefore that mCPP decreases food intake via an agonist action at the 5-HT_{2C} receptor.

Other compounds which have been proposed as 5-HT_{2C} receptor agonists for use in the treatment of obesity include the substituted 1-aminoethyl indoles disclosed in EP-A-
35 0655440. CA-2132887 and CA-2153937 disclose that tricyclic 1-aminoethylpyrrole

derivatives and tricyclic 1-aminoethyl pyrazole derivatives bind to 5-HT_{2C} receptors and may be used in the treatment of obesity. WO-A-98/30548 discloses aminoalkylindazole compounds as 5-HT_{2C} agonists for the treatment of CNS diseases and appetite regulation disorders. WO 0035922 discloses 2,3,4,4a-tetrahydro-1H-pyrazino[1,2-a]quinoxalin-5(6H)ones as 5HT_{2C} agonists. Aralkyloxycarbonyl-substituted piperazine derivatives have been repeatedly described as nitrogen-protected piperazine synthetic intermediates (e.g. Org. Lett., 2000, 2(8), 1049-1051.

It is an object of this invention to provide selective, directly acting 5HT₂ receptor ligands for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide directly acting ligands selective for 5-HT_{2B} and/or 5-HT_{2C} receptors, for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide selective, directly acting 5-HT_{2C} receptor ligands, preferably 5-HT_{2C} receptor agonists, for use in therapy and particularly for use as anti-obesity agents.

In the present description the term "alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, preferably a straight or branched-chain alkyl group with 1-4 carbon atoms. Examples of straight-chain and branched C₁-C₈ alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, preferably methyl, ethyl, propyl and isopropyl. Particularly preferred are methyl and ethyl.

The term "cycloalkyl", alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and preferably a cycloalkyl ring with 3 to 6 carbon atoms. Examples of C₃-C₈ cycloalkyl are cyclopropyl, methyl-cyclopropyl, dimethylcyclopropyl, cyclobutyl, methyl-cyclobutyl, cyclopentyl, methyl-cyclopentyl, cyclohexyl, methylcyclohexyl, dimethyl-cyclohexyl, cycloheptyl and cyclooctyl, preferably cyclopropyl and particularly cyclopentyl.

The term "alkoxy", alone or in combination, signifies a group of the formula alkyl-O- in which the term "alkyl" has the previously given significance, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.butoxy and tert.butoxy, preferably methoxy and ethoxy.

The term "cycloalkoxy", alone or in combination, signifies a group of the formula cycloalkyl-O- in which the term "cycloalkyl" has the previously given significance, such as cyclohexyloxy.

5 The term "aryloxy", alone or in combination, signifies a group of the formula aryl-O- in which the term "aryl" has the previously given significance. Phenyl is an example of such an aryloxy group.

The term "carbonyl" refer to a group of the formula -C(O)- .

The term "aryl", alone or in combination, signifies a phenyl or naphthyl group such as 1-naphthyl and 2-naphthyl. Preferred is phenyl.

10 The term "heteroaryl", alone or in combination, signifies an aromatic 5- or 6-membered ring comprising 1 to 3 atoms independently selected from nitrogen, oxygen or sulfur such as e.g. furyl, pyridyl, 1,2-, 1,3- and 1,4-diazinyl, thienyl, isoxazolyl, oxazolyl and pyrrolyl. Preferred examples are pyridyl, thienyl, pyrazinyl and furyl. Particularly preferred are pyridyl and thienyl.

15 The term "aralkyl", alone or in combination, signifies an alkyl or cycloalkyl group as previously defined in which one or several, preferably one hydrogen atom has been replaced by an aryl group as previously defined. Preferred is benzyl.

The term "3- to 8-membered carbocyclic ring " as used for the definition of R^1 and R^2 signifies a 3- to 8-membered, preferably 3 to 6 membered cycloalkane ring. Examples
20 are cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane and cyclooctane, preferably cyclopropane.

The term "5- to 7-membered carbocyclic ring " as used for the definition of A^2 signifies a cycloalkane ring with 5 to 7, preferably 6 carbon atoms optionally substituted with alkyl, alkoxy or halogen. Examples are cyclopentane, methyl-cyclopentane,
25 cyclohexane, methylcyclohexane, dimethyl-cyclohexane and cycloheptane preferably cyclohexane.

The term "aralkoxy", alone or in combination, signifies an alkoxy or cycloalkoxy group as previously defined in which one or several, preferably one hydrogen atom has been replaced by an aryl group as previously defined. Preferred is benzyloxy.

The term "nitro", alone or in combination, signifies a -NO_2 group.

The term "cyano", alone or in combination, signifies a -CN group.

The term "alkoxycarbonyl", alone or in combination, signifies an alkoxy- C(O) -group, wherein alkoxy is defined as before.

5 The term "cycloalkoxycarbonyl", alone or in combination, signifies an cycloalkoxy- C(O) - group, wherein cycloalkoxy is defined as before.

The term "aryloxycarbonyl", alone or in combination, signifies an aryloxy- C(O) -group, wherein aryloxy is defined as before.

10 The term "aralkoxycarbonyl", alone or in combination, signifies an aralkoxy- C(O) -group, wherein aralkoxy is defined as before.

The term "heteroaryloxycarbonyl", alone or in combination, signifies a heteroaryl- O-C(O) - group, wherein heteroaryl is defined as before.

15 The term "amino", alone or in combination, signifies a primary, secondary or tertiary amino group bonded via the nitrogen atom, with the secondary amino group carrying an alkyl or cycloalkyl substituent and the tertiary amino group carrying two similar or different alkyl or cycloalkyl substituents or the two nitrogen substituents together forming a ring, such as, for example, -NH_2 , methylamino, ethylamino, dimethylamino, diethylamino, methyl-ethylamino, pyrrolidin-1-yl or piperidino etc., preferably amino, dimethylamino and diethylamino and particularly primary amino.

20 The term "halogen" signifies fluorine, chlorine, bromine or iodine and preferably fluorine, chlorine or bromine and particularly fluorine and chlorine.

The term "carbamoyl" refers to a group of the formula -N(R')-C(O)- , wherein R' means hydrogen, alkyl, cycloalkyl, aryl, aralkyl or heteroaryl, preferably hydrogen, alkyl or cycloalkyl. Most preferred is hydrogen.

25 Examples of pharmaceutically usable salts of the compounds of formula I are salts with physiologically compatible mineral acids such hydrochloric acid, sulfuric acid or phosphoric acid; or with organic acids such as methanesulphonic acid, acetic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. Preferred salts of compounds of formula I are hydrochloride salts, succinate

salts and fumarate salts. The compounds of formula I can also form salts with physiologically compatible bases. Examples of such salts are alkali metal, alkali earth metal, ammonium and alkylammonium salts such as the Na, K, Ca or tetramethylammonium salt. The compound of formula I can also be present in the form of zwitterions.

5 The invention expressly includes pharmaceutically suitable derivatives of the compounds of formula I. For example hydroxy groups of compounds of formula I can be esterified. Examples of such esters are formate, acetate, propionate, butyrate, isobutyrate, valerate, 2-methylbutyrate, isovalerate and N,N-dimethylaminoacetate. Preferred esters are acetate and N,N-dimethylaminoacetate.

10 Also included are pharmaceutically usable solvates of compounds according to formula I such as for example hydrates. The solvation can be effected in the course of the manufacturing process or can take place e.g. as a consequence of hygroscopic properties of an initially anhydrous compound of formula I (hydration).

15 The term "lipase inhibitor" refers to compounds that are capable of inhibiting the action of lipases, for example gastric and pancreatic lipases. For example orlistat and lipstatin as described in U.S. Patent No. 4,598,089 are potent inhibitor of lipases. Lipstatin is a natural product of microbial origin, and orlistat is the result of a hydrogenation of lipstatin. Other lipase inhibitors include a class of compound commonly referred to as panclicins. Panclicins are analogues of orlistat (Mutoh et al, 1994). The term "lipase
20 inhibitor" refers also to polymer bound lipase inhibitors for example described in International Patent Application WO99/34786 (Geltex Pharmaceuticals Inc.). These polymers are characterised in that they have been substituted with one or more groups that inhibit lipases. The term "lipase inhibitor" also comprises pharmaceutically acceptable salts of these compounds. The term "lipase inhibitor" preferably refers to orlistat.

25 Orlistat is a known compound useful for the control or prevention of obesity and hyperlipidemia. See, U.S. Patent No. 4,598,089, issued July 1, 1986, which also discloses processes for making orlistat and U.S. Patent No. 6,004,996, which discloses appropriate pharmaceutical compositions. Further suitable pharmaceutical compositions are described for example in International Patent Applications WO 00/09122 and WO 00/09123.
30 Additional processes for the preparation of orlistat are disclosed in European Patent Applications Publication Nos. 185,359, 189,577, 443,449, and 524,495.

Orlistat is preferably orally administered from 60 to 720 mg per day in divided doses two to three times per day. Preferred is wherein from 180 to 360 mg, most preferably 360

mg per day of a lipase inhibitor is administered to a subject, preferably in divided doses two or, particularly, three times per day. The subject is preferably an obese or overweight human, i.e. a human with a body mass index of 25 or greater. Generally, it is preferred that the lipase inhibitor be administered within about one or two hours of ingestion of a meal
5 containing fat. Generally, for administering a lipase inhibitor as defined above it is preferred that treatment be administered to a human who has a strong family history of obesity and has obtained a body mass index of 25 or greater.

Orlistat can be administered to humans in conventional oral compositions, such as, tablets, coated tablets, hard and soft gelatin capsules, emulsions or suspensions.
10 Examples of carriers which can be used for tablets, coated tablets, dragées and hard gelatin capsules are lactose, other sugars and sugar alcohols like sorbitol, mannitol, maltodextrin, or other fillers; surfactants like sodium lauryl sulfate, Brij 96, or Tween 80; disintegrants like sodium starch glycolate, maize starch or derivatives thereof; polymers like povidone, crospovidone; talc; stearic acid or its salts and the like. Suitable carriers for soft gelatin
15 capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Moreover, the pharmaceutical preparations can contain preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating agents and antioxidants. They can also contain still other therapeutically valuable
20 substances. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods known in the pharmaceutical art. Preferably, orlistat is administered according to the formulation shown in the Examples and in U.S. Patent No. 6,004,996, respectively.

The compounds of formula I can contain several asymmetric centres and can be
25 present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbent or
30 eluent).

Preferred compounds according to formula I are those, wherein R^3 and R^4 are independently selected from hydrogen and alkyl, preferably methyl. Particularly preferred are compound of formula I, wherein R^3 and R^4 are both hydrogen or wherein R^3 and R^4

are both alkyl. Most preferred are compounds according to formula I, wherein R^3 and R^4 are both hydrogen or wherein R^3 and R^4 are both methyl.

Further preferred compounds of formula I are those, wherein A^1 is sulfur.
Particularly preferred are those, wherein A^1 is oxygen.

5 Also preferred are compounds of formula I, wherein R^1 and R^2 are independently selected from hydrogen, alkyl, cycloalkyl, aryl and aralkyl or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 8-membered cycloalkyl ring which is optionally substituted with alkyl. A particularly preferred embodiment of the invention comprises compounds of formula I, wherein R^1 and R^2 are independently selected from
10 hydrogen, alkyl and aryl, preferably hydrogen, methyl and phenyl. Most preferred are those compounds, wherein R^1 and R^2 are both hydrogen.

Likewise preferred are compounds of the present invention, wherein A^2 is phenyl, naphthalenyl, cycloalkyl, pyridyl, thienyl, pyrazinyl or furyl, each optionally substituted with one or more, preferably one to four substituents, independently selected from
15 halogen, alkyl, cycloalkyl, aryl, aralkyl, alkoxy, aralkoxy, aryloxy, hydroxy, cyano, nitro, amino, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heteroaryloxycarbonyl and carbamoyl, wherein alkyl, cycloalkyl, aryl, aralkyl, alkoxy, aralkoxy, aryloxy, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl and heteroaryloxycarbonyl are optionally substituted with one to three substituents
20 independently selected from alkyl, alkoxy, halogen and nitro, or two substituents of aryl, heteroaryl or cycloalkyl form together with the carbon atoms to which they are attached a 5- to 7-membered carbocyclic ring which is optionally substituted with alkyl, alkoxy or halogen.

Preferred are compounds according to formula I, wherein A^2 is phenyl,
25 naphthalenyl, cyclohexyl, pyridyl or thienyl each optionally substituted with one or more, preferably one to four substituents independently selected from halogen, alkyl, cycloalkyl, aryl, aralkyl, alkoxy, aralkoxy, aryloxy, hydroxy, cyano, nitro, amino, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heteroaryloxycarbonyl and carbamoyl, wherein alkyl, cycloalkyl, aryl, aralkyl, alkoxy, aralkoxy, aryloxy, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl and
30 heteroaryloxycarbonyl are optionally substituted with one to three substituents independently selected from alkyl, alkoxy, halogen and nitro. Particularly preferred examples of the above substituents of phenyl, naphthalenyl, cyclohexyl, pyridyl and thienyl

are trifluoromethoxyl, fluoro, chloro, bromo, nitro, phenylmethoxy, trifluoromethyl, methyl, tert-butyl, difluoromethoxy, cyano, methoxycarbonyl, benzyloxy, fluoro-benzyloxy, chlorobenzyloxy and nitrobenzyloxy.

5 Particularly preferred are compounds of formula I are those, wherein A² is phenyl, naphthalenyl, cyclohexyl, pyridyl or thienyl each optionally substituted with one or more, preferably one to four substituents independently selected from halogen, alkyl, aryl, alkoxy, aralkoxy, cyano, nitro, alkoxycarbonyl, wherein alkyl, alkoxy, aralkoxy and alkoxycarbonyl are optionally substituted with one to three substituents independently selected from halogen and nitro.

10 Another preferred aspect of the invention are compounds of formula I, wherein A² is phenyl optionally substituted with one to five, preferably one to three substituents independently selected from halogen, alkyl, aryl, alkoxy, aralkoxy, cyano, nitro, alkoxycarbonyl, wherein alkyl, alkoxy and aralkoxy optionally substituted with one to three substituents independently selected from halogen and nitro.

15 A further preferred object of the present invention are compounds according to formula I, wherein n is 1.

Examples of preferred compounds of formula I are:

- Piperazine-1-carboxylic acid 4-trifluoromethoxy-benzyl ester;
- piperazine-1-carboxylic acid 3,4-difluoro-benzyl ester;
- 20 piperazine-1-carboxylic acid 4-fluoro-benzyl ester;
- piperazine-1-carboxylic acid 4-bromo-benzyl ester;
- piperazine-1-carboxylic acid 2-trifluoromethoxy-benzyl ester;
- piperazine-1-carboxylic acid 2-chloro-5-nitro-benzyl ester;
- piperazine-1-carboxylic acid 2-chloro-benzyl ester;
- 25 piperazine-1-carboxylic acid biphenyl-4-ylmethyl ester;
- piperazine-1-carboxylic acid 3-methoxy-benzyl ester;

- piperazine-1-carboxylic acid 3-trifluoromethyl-benzyl ester;
- piperazine-1-carboxylic acid 4-trifluoromethyl-benzyl ester;
- piperazine-1-carboxylic acid naphthalen-2-ylmethyl ester;
- piperazine-1-carboxylic acid naphthalen-1-ylmethyl ester;
- 5 piperazine-1-carboxylic acid 2-methyl-benzyl ester;
- piperazine-1-carboxylic acid 2,4-dichloro-benzyl ester;
- piperazine-1-carboxylic acid 2,6-dichloro-benzyl ester;
- piperazine-1-carboxylic acid 4-tert-butyl-benzyl ester;
- piperazine-1-carboxylic acid 2-fluoro-4-trifluoromethyl-benzyl ester;
- 10 piperazine-1-carboxylic acid 2,4-difluoro-benzyl ester;
- piperazine-1-carboxylic acid 2-chloro-4-fluoro-benzyl ester;
- piperazine-1-carboxylic acid 4-fluoro-2-trifluoromethyl-benzyl ester;
- piperazine-1-carboxylic acid 4-difluoromethoxy-benzyl ester;
- piperazine-1-carboxylic acid 2,4-dimethyl-benzyl ester;
- 15 piperazine-1-carboxylic acid cyclohexylmethyl ester;
- piperazine-1-carboxylic acid 2-fluoro-benzyl ester;
- cis-2,6-dimethyl-piperazine-1-carboxylic acid 4-chloro-benzyl ester;
- cis-2,6-dimethyl-piperazine-1-carboxylic acid 3-cyano-benzyl ester;
- cis-2,6-dimethyl-piperazine-1-carboxylic acid 4-methoxycarbonyl-benzyl ester;
- 20 piperazine-1-carboxylic acid 4-cyano-benzyl ester;
- piperazine-1-carboxylic acid 2-trifluoromethyl-benzyl ester;
- piperazine-1-carboxylic acid 4-chloro-2-fluoro-benzyl ester;

- piperazine-1-carbothioic acid S-(4-benzyloxy-benzyl) ester;
- piperazine-1-carbothioic acid S-(4-bromo-benzyl) ester;
- piperazine-1-carbothioic acid S-(4-trifluoromethoxy-benzyl) ester;
- piperazine-1-carbothioic acid S-(4-fluoro-benzyl) ester;
- 5 piperazine-1-carbothioic acid S-(2,4-difluoro-benzyl) ester;
- piperazine-1-carbothioic acid S-(4-methoxy-benzyl) ester;
- piperazine-1-carbothioic acid S-(2,4-dimethyl-benzyl) ester;
- piperazine-1-carbothioic acid S-(2-fluoro-4-trifluoromethyl-benzyl) ester;
- piperazine-1-carbothioic acid S-[4-(4-fluoro-benzyloxy)-benzyl] ester;
- 10 piperazine-1-carboxylic acid 4-benzyloxy-benzyl ester;
- piperazine-1-carboxylic acid 4-(4-fluoro-benzyloxy)-benzyl ester;
- piperazine-1-carboxylic acid 4-methoxy-benzyl ester;
- piperazine-1-carboxylic acid benzhydryl ester;
- (RS)-piperazine-1-carboxylic acid 1-phenyl-ethyl ester;
- 15 piperazine-1-carboxylic acid phenethyl ester;
- cis-2,6-dimethylpiperazine-1-carboxylic acid 5-[2-(3-chlorobenzyloxy)]pyridyl-methyl ester;
- piperazine-1-carboxylic acid 5-[2-(3-chlorobenzyloxy)]pyridyl-methyl ester;
- cis-2,6-dimethylpiperazine-1-carboxylic acid 2-(2-thienyl)ethyl ester;
- 20 cis-2,6-dimethylpiperazine-1-carboxylic acid 2-fluoro-benzyl ester;
- piperazine-1-carbothioic acid S-[4-(3-nitrobenzyl)oxy]benzyl ester;
- piperazine-1-carboxylic acid 3-(2-phenethyloxy)-benzyl ester.

Examples of particularly preferred compounds of formula I are:

- piperazine-1-carboxylic acid 4-trifluoromethoxy-benzyl ester;
- piperazine-1-carboxylic acid 2-chloro-benzyl ester;
- 5 piperazine-1-carboxylic acid 4-difluoromethoxy-benzyl ester;
- piperazine-1-carboxylic acid 2-fluoro-benzyl ester;
- cis-2,6-dimethyl-piperazine-1-carboxylic acid 4-chloro-benzyl ester;
- piperazine-1-carbothioic acid S-(4-benzyloxy-benzyl) ester;
- piperazine-1-carbothioic acid S-(2,4-difluoro-benzyl) ester;
- 10 piperazine-1-carbothioic acid S-(4-methoxy-benzyl) ester;
- piperazine-1-carbothioic acid S-[4-(4-fluoro-benzyloxy)-benzyl] ester;
- piperazine-1-carboxylic acid 4-(4-fluoro-benzyloxy)-benzyl ester;
- cis-2,6-dimethylpiperazine-1-carboxylic acid 2-(2-thienyl)ethyl ester and
- cis-2,6-dimethylpiperazine-1-carboxylic acid 2-fluoro-benzyl ester.

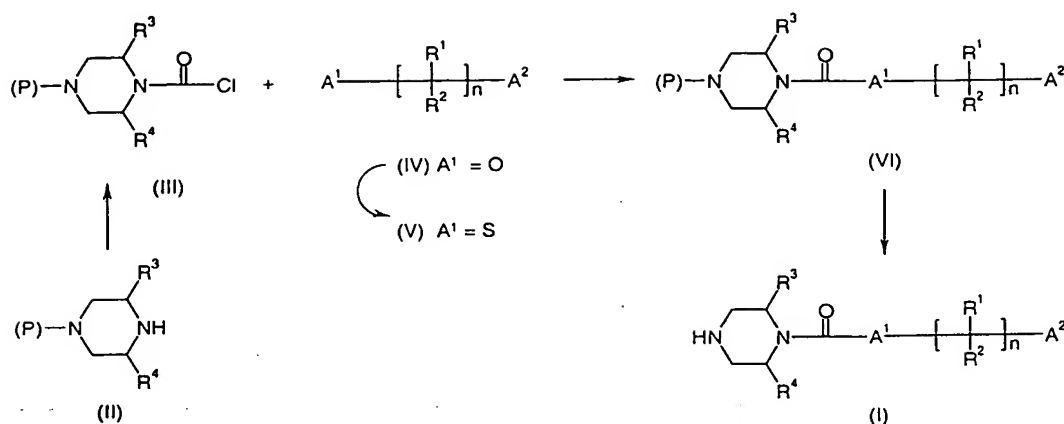
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Processes for the manufacture of the compounds according to formula I are an object of the present invention. The substituents and indices used in the following schemes have the significance given above unless indicated to the contrary.

- 20 Compounds of formula (I) where R^1 to R^4 , A^1 , A^2 and n are as previously defined may be conveniently prepared according to Reaction Scheme 1.

25

Reaction Scheme 1



A compound of formula (VI) can be prepared by reaction of the piperazine carbamoyl chloride (III) with an alcohol (IV) or thiol (V) in the presence of a suitable base such as sodium hydride, triethylamine, PS-BEMP or pyridine in a solvent such as acetonitrile, N-methylpyrrolidinone, dimethyl formamide, tetrahydrofuran or dichloromethane. The piperazine may be protected using a suitable protecting group (P) e.g. tert-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, allyloxycarbonyl, trimethylsilyl, 3,4-dimethoxybenzyl and trityl, preferably tert-butoxycarbonyl and 9-fluorenylmethoxycarbonyl.

The protected piperazine-carbamoyl chloride (III) may be synthesised from a protected piperazine (II) by treatment with a reagent such as phosgene, diphosgene or triphosgene in the presence of a base such as pyridine in a suitable solvent, for instance dichloromethane. Where necessary, protected piperazines (II) can be synthesised from commercially available monoalkyl- or dialkyl-aminopiperazines by treatment with reagents known to introduce the desired protecting group e.g. di-tert-butyl dicarbonate or 9-fluorenylmethyl chloroformate. Mono or dialkyl-piperazines may be prepared by those skilled in the art via a variety of methods which includes, but is not limited to: reduction of mono or dialkylpyrazines using e.g. catalytic hydrogenation or dissolved metal reagents; alkylation of ethylene diamine and alkylated analogues with e.g. alkyl-substituted 1,2-dihaloethane compounds, alkyl-substituted 1,2-dihydroxyethane compounds or alkyl-substituted ethane-1,2-dialkylsulfonate compounds; reduction of a monoalkyl substituted

2,5-diketopiperazine with e.g. sodium or lithium borohydride or lithium aluminium hydride.

The alcohol (IV) may be commercially available or alternatively may be synthesised via reduction of an aldehyde, carboxylic acid, ester or amide derivative with a reagent such as sodium or lithium borohydride or lithium aluminium hydride in a suitable solvent or alternatively via Grignard addition of alkyl- or aryl-magnesium halides or alkyl- or aryl-lithium nucleophiles to aldehydes or carboxylic esters or amides. The aldehydes, carboxylic acids, esters and amides may be commercially available or synthesised according to methods known to those skilled in the art. Such methods include but are not limited to formylation of an aryl or heteroaryl containing starting-material, vicarious nucleophilic substitution, hydrolysis of an alkyl halide or oxidation of an aryl-methyl (tolyl) group.

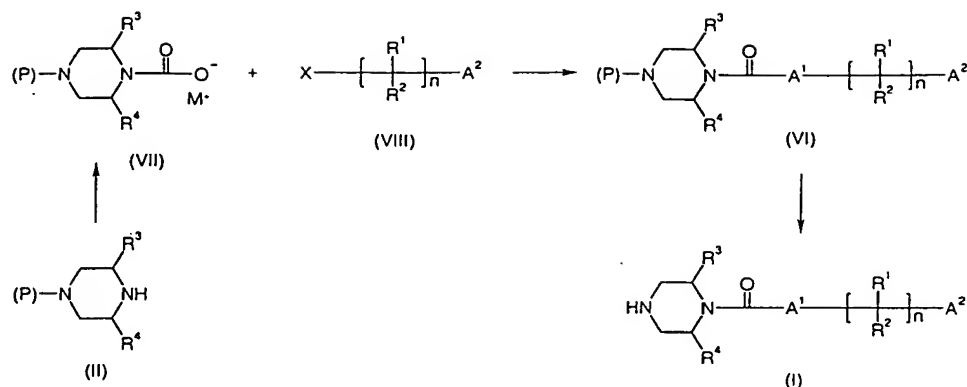
Thiols of formula (V) may be prepared from (IV) by a variety of methods e.g. displacement of an activated derivative of the hydroxyl of (IV) with a sulfur nucleophile such as thiolacetic acid followed by treatment with a reducing agent such as lithium aluminium hydride. Activated hydroxyl derivatives include but are not limited to mesylates, tosylates and in situ activation with phosphorus compounds such as triphenylphosphine.

Thiols of formula (V) may be replaced by xanthogenates, which are prepared *in situ* from alcohol (IV) with carbon disulfide and a base such as sodium or potassium hydroxide in a solvent such as tetrahydrofuran or acetone.

Compounds of formula (I) may be prepared from compounds of formula (VI) by reaction with a reagent known to selectively remove the protecting group (P) e.g. tert-butoxycarbonyl and 3,4-dimethoxybenzyl may be removed using an acid such as hydrochloric acid or trifluoroacetic acid and 9-fluorenylmethoxycarbonyl may be removed by treatment with a base such as morpholine.

Alternatively compounds of formula (I) where $A^1 = O$ may be prepared via Reaction Scheme (2) below.

Reaction Scheme 2

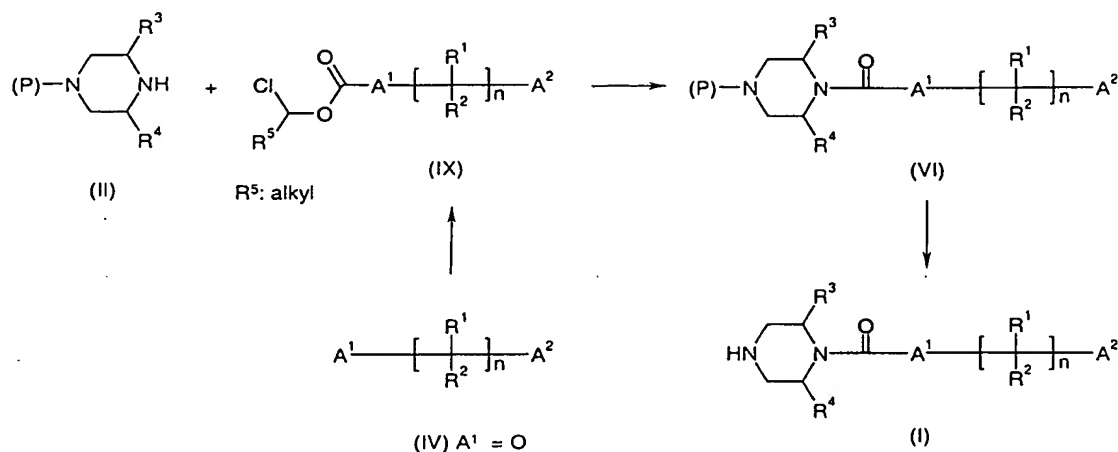


Reaction of a piperazine (II) with carbon dioxide in the presence of a base such as tetraalkylammonium (for alkyl preferably ethyl or butyl) hydrogencarbonate or potassium hydride or butyl-lithium or a metal such as lithium may produce the piperazine-carboxylate (VII). Treatment of (VII) with halide (VIII) (X means Cl, Br or I) in a suitable solvent may give a compound of formula (VI) where A¹ = O. Halides of formula (VIII) may be synthesised if not commercially available by methods known to those skilled in the art. Such methods include, but are not limited to: conversion of an alcohol of formula (IV) where A¹ = O via treatment with triphenylphosphine and a halogen such as bromine; formation and displacement of an alkyl or arylsulfonate such as mesylate or tosylate with a halide salt such as sodium bromide in a solvent such as tetrahydrofuran or acetone and halogenation of an aralkyl or heteroaralkyl compound with a reagent such as N-bromosuccinimide optionally in the presence of a co-reagent such as AIBN (2,2'-azobisisobutyronitrile) or benzoyl peroxide. Compounds of formula (VI) can be transformed into compounds of formula (I) by methods as described above in Reaction Scheme 1.

If, in any of the other processes mentioned herein, R¹, R², R³, R⁴ and the substituent groups attached to A² are other than the one required, the substituent group may be converted to the desired substituent by known methods. R¹, R², R³, R⁴ and the substituent groups attached to A² may also need protecting against the conditions under which the reaction is carried out. In such a case, the protecting group may be removed after the reaction has been completed.

Alternatively compounds of formula (I) where $A^1 = O$ may be prepared via Reaction Scheme (3) below.

Reaction Scheme 3



5

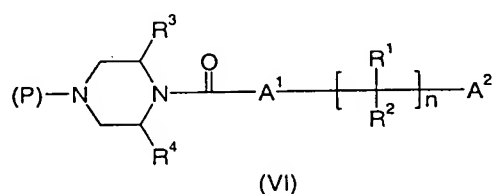
A compound of formula (VI) can be prepared by reaction of the piperazine (II) with an activated derivative (IX) of alcohol (IV) optionally in the presence of a suitable base such as triethylamine, PS-BEMP or pyridine in a solvent such as acetonitrile, N-methylpyrrolidinone, dimethyl formamide, tetrahydrofuran or dichloromethane. The piperazine may be protected using a suitable protecting group (P) e.g. tert-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, allyloxycarbonyl, trimethylsilyl, 3,4-dimethoxybenzyl and trityl, preferably tert-butoxycarbonyl and 9-fluorenylmethoxycarbonyl.

The activated derivative (IX) may be synthesised from alcohol (IV) with 1-chloroalkyl chloroformate, preferably 1-chloroethyl chloroformate, in the presence of a suitable base such as triethylamine, PS-BEMP or pyridine in a solvent such as acetonitrile, N-methylpyrrolidinone, dimethyl formamide, tetrahydrofuran or dichloromethane.

Compounds of formula (I) may be prepared from compounds of formula (VI) by reaction with a reagent known to selectively remove the protecting group (P) e.g. tert-butoxycarbonyl and 3,4-dimethoxybenzyl may be removed using an acid such as hydrochloric acid or trifluoroacetic acid and 9-fluorenylmethoxycarbonyl may be removed by treatment with a base such as morpholine.

The processes as described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base, an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from basic compounds.

10 A further object of the present invention is the process for the preparation of a compound according to formula I comprising the deprotection of a compound according to formula



wherein R^1 to R^4 , A^1 , A^2 and n are defined as before and (P) is a nitrogen protecting group.

15 Examples of nitrogen protecting groups are tert-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, allyloxycarbonyl, trimethylsilyl, 3,4-dimethoxybenzyl and trityl, preferably tert-butoxycarbonyl and 9-fluorenylmethoxycarbonyl.

Another preferred aspect of this invention are the following intermediates:

20 Cis-4-chlorocarbonyl-2,6-dimethyl-piperazine-1-carboxylic acid tert-butyl ester;
Piperazine-1,4-dicarboxylic acid tert-butyl ester 4-trifluoromethoxy-benzyl ester;
Piperazine-1,4-dicarboxylic acid tert-butyl ester 2-fluoro-benzyl ester;
4-(4-Benzyloxy-benzylsulfanylcabonyl)-piperazine-1-carboxylic acid tert-butyl ester;
4-[4-(4-Fluoro-benzyloxy)-benzylsulfanylcabonyl]-piperazine-1-carboxylic acid tert-
25 butyl ester;

Piperazine-1,4-dicarboxylic acid 4-benzyloxy-benzyl ester 9H-fluoren-9-ylmethyl ester;

Piperazine-1,4-dicarboxylic acid 9H-fluoren-9-ylmethyl ester 4-(4-fluoro-benzyloxy)-benzyl ester;

Piperazine-1,4-dicarboxylic acid 9H-fluoren-9-ylmethyl ester 4-methoxy-benzyl ester;

5 Piperazine-1,4-dicarboxylic acid benzhydryl ester 9H-fluoren-9-ylmethyl ester;

(RS)-Piperazine-1,4-dicarboxylic acid 9H-fluoren-9-ylmethyl ester 1-phenyl-ethyl ester;

cis-2,6-Dimethylpiperazine-1,4-dicarboxylic acid 5-(2-chloropyridyl)methyl ester tert-butyl ester;

10 cis-2,6-Dimethylpiperazine-1,4-dicarboxylic acid 5-[2-(3-chlorobenzyloxy)]pyridyl-methyl ester tert-butyl ester;

Piperazine-1,4-dicarboxylic acid 5-[2-(3-chlorobenzyloxy)]pyridyl-methyl ester tert-butyl ester;

[(4-tert-Butyl-dimethylsilyloxy)benzylsulfanylcarbonyl]-piperazine-4-carboxylic acid tert-butyl ester;

15 Piperazine-1,4-dicarboxylic acid (3-tert-butyldimethylsilyloxy)benzyl ester tert-butyl ester;

Piperazine-1,4-dicarboxylic acid (3-hydroxy)benzyl ester tert-butyl ester;

Piperazine-1,4-dicarboxylic acid 3-(2-phenylethoxy)benzyl ester tert-butyl ester;

4-(4-Fluoro-benzyloxy)-phenyl-methanethiol;

(RS)-Carbonic acid 4-benzyloxy-benzyl ester 1-chloro-ethyl ester;

20 (RS)-Carbonic acid 1-chloro-ethyl ester 4-(4-fluoro-benzyloxy)-benzyl ester;

(RS)-Carbonic acid 1-chloro-ethyl ester 4-methoxy-benzyl ester;

(RS)-Carbonic acid benzhydryl ester 1-chloro-ethyl ester;

(RS)-Carbonic acid 1-chloro-ethyl ester 1-phenyl-ethyl ester.

The compounds according to formula I for as therapeutically active substances are a further object of the invention.

Also an object of the invention are compounds of formula I as described above for the production of medicaments for the prophylaxis and therapy of illnesses which are
5 caused by disorders associated with the 5-HT₂ receptor, particularly with the 5-HT_{2a}, 5-HT_{2b} or 5-HT_{2c} subtype. Most preferred is the 5-HT_{2c} subtype.

Likewise an object of the invention are pharmaceutical composition comprising a compound of formula I and a therapeutically inert carrier.

A further object of the invention are compounds in accordance with formula I for
10 the production of medicaments for the treatment and prophylaxis of eating disorders and obesity.

An object of the invention is the use of compounds in accordance with formula I for the production of medicaments for the treatment and prophylaxis of disorders of the central nervous system, cardiovascular disorders, gastrointestinal disorders, diabetes
15 insipidus and sleep apnoea.

Particularly an object of the invention is the above use, wherein the disorders of the central nervous system are selected from depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions
20 associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, bulimia, anorexia nervosa, premenstrual tension, trauma, stroke, neurodegenerative diseases,
25 encephalitis and meningitis.

A further preferred embodiment of the present invention is the above mentioned use of the compounds according to formula I, wherein the cardiovascular disorder is thrombosis.

Also preferred is the mentioned use of the compounds according to formula I,
30 wherein the gastrointestinal disorder is dysfunction of gastrointestinal motility.

A further object of the invention are compounds in accordance with formula I, when manufactured according to the described process.

A further embodiment of the present invention is a method for the treatment and prophylaxis of disorders of the central nervous system, cardiovascular disorders, gastrointestinal disorders, diabetes insipidus, and sleep apnoea., which method comprises administering an effective amount of a compound of formula I as described. Preferred is
5 this method, wherein the disorders of the central nervous system are selected from depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural
10 disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, bulimia, anorexia nervosa, premenstrual tension, trauma, stroke, neurodegenerative diseases, encephalitis and meningitis.

A preferred object of the invention is a method for the treatment and prophylaxis of
15 eating disorders and obesity, which method comprises administering an effective amount of a compound of formula I.

A further preferred object is a method of treatment of obesity in a human in need of such treatment which comprises administration to the human a therapeutically effective amount of a compound according to any one of claims 1 to 11 and a therapeutically
20 effective amount of a lipase inhibitor, particularly, wherein the lipase inhibitor is orlistat.

Also an object of the invention are the method as described above for the simultaneous, separate or sequential administration.

A further object of the invention is the use of a compound of formula I in the manufacture of a medicament for the treatment and prevention of obesity in a patient who
25 is also receiving treatment with a lipase inhibitor and particularly, wherein the lipase inhibitor is orlistat.

Also an object of the invention is the pharmaceutical composition comprising a compound of formula I, a therapeutically inert carrier and further a therapeutically effective amount of a lipase inhibitor, particularly, wherein the lipase inhibitor is orlistat.

30 The compounds of formula (I) may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT₂ receptor function. The compounds may act as receptor agonists or antagonists. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_{2b} and/or

5-HT_{2c} receptor function. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders where a 5-HT_{2c} receptor agonist is required.

5 The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (*e.g.*, intravenous, intramuscular or subcutaneous) transdermal or rectal administration or in a form suitable for administration by inhalation or insufflation.

10 For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.* pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropylmethylcellulose); fillers (*e.g.* lactose, microcrystalline cellulose or calcium phosphate); lubricants (*e.g.* magnesium stearate, talc
15 or silica); disintegrants (*e.g.* potato starch or sodium starch glycollate); or wetting agents (*e.g.* sodium lauryl sulfate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by
20 conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.* sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (*e.g.* lecithin or acacia); non-aqueous vehicles (*e.g.* almond oil, oily esters or ethyl alcohol); and preservatives (*e.g.* methyl or propyl *p*-hydroxybenzoates or sorbic acid).

25 For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

30 The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form *e.g.* in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents.

Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, *e.g.* sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional
5 suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable
10 propellant, *e.g.* dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from
15 gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (*e.g.*, obesity) is 0.1 to 500 mg of the active ingredient per unit dose
20 which could be administered, for example, 1 to 4 times per day.

The invention will now be described in detail with reference to the following examples. It will be appreciated that the invention is described by way of example only and modification of detail may be made without departing from the scope of the
25 invention.

Assay Procedures

1. Binding to serotonin receptors

The binding of compounds of formula (I) to serotonin receptors was determined *in vitro* by standard methods. The preparations were investigated in accordance with the assays given hereinafter.

Method (a): For the binding to the 5-HT_{2C} receptor the 5-HT_{2C} receptors were radiolabeled with [³H]-5-HT. The affinity of the compounds for 5-HT_{2C} receptors in a CHO cell line was determined according to the procedure of D. Hoyer, G. Engel and H.O. Kalkman, *European J. Pharmacol.*, 1985, 118, 13-23.

Method (b): For the binding to the 5-HT_{2B} receptor the 5-HT_{2B} receptors were radiolabeled with [³H]-5-HT. The affinity of the compounds for human 5-HT_{2B} receptors in a CHO cell line was determined according to the procedure of K. Schmuck, C. Ullmer, P. Engels and H. Lubbert, *FEBS Lett.*, 1994, 342, 85-90.

Method (c): For the binding to the 5-HT_{2A} receptor the 5-HT_{2A} receptors were radiolabeled with [¹²⁵I]-DOI. The affinity of the compounds for 5-HT_{2A} receptors in a CHO cell line was determined according to the procedure of D. J. McKenna and S. J. Peroutka, *J. Neurosci.*, 1989, 9, 3482-90.

The thus determined activity of the compound of the Example is shown in Table 1.

Table 1

Compound	Method (a) Ki (2C)	Method (b) Ki (2B)	Method (c) Ki (2A)
Example 32	15 nM	371 nM	6 nM
Example 22	44 nM	4017 nM	44 nM

Preferred Ki (2C) values are below 10000 nM; especially preferred Ki (2C) values are below 1000 nM, particularly preferred Ki (2C) values are below 100 nM. Most preferred Ki (2C) values are below 50 nM.

2. Functional activity

The functional activity of compounds of formula (I) was assayed using a Fluorimetric Imaging Plate reader (FLIPR). CHO cells expressing the human 5-HT_{2C} or human 5-HT_{2A} receptors were counted and plated into standard 96 well microtitre plates on the day before testing to give a confluent monolayer. The cells were then dye loaded with the calcium sensitive dye, Fluo-3-AM. Unincorporated dye was removed using an automated cell washer to leave a total volume of 100 µL/well of assay buffer (Hanks balanced salt solution containing 20 mM Hepes and 2.5 mM probenecid). The drug (dissolved in 50 µL of the assay buffer) was added at a rate of 70 µL/sec to each well of the FLIPR 96 well plate during fluorescence measurements. The measurements were taken at 1 sec intervals and the maximum fluorescent signal was measured (approx 10-15 secs after drug addition) and compared with the response produced by 10 µM 5-HT (defined as 100%) to which it was expressed as a percentage response (relative efficacy). Dose response curves were constructed using Graphpad Prism (Graph Software Inc.).

Table 2

Compound	h5-HT _{2C}		h5-HT _{2A}		h5-HT _{2B}	
	EC ₅₀ (nM)	Relative Efficacy (%)	EC ₅₀ (nM)	Relative Efficacy (%)	EC ₅₀ (nM)	Relative Efficacy (%)
Example 32	38	65%	561	22%	4001	28%
Example 22	100	56%	218	24%	458	55%

The compounds of formula (I) have activity at the h5-HT_{2C} receptor in the range of 10,000 to 0.1 nM.

Preferred activities at the h5-HT_{2C} receptor are below 10000nM; especially preferred below 1000nM, particularly preferred activities are below 100nM. Most preferred activity at the h5-HT_{2C} receptor are below 50 nM.

The compounds of formula (I) have maximum functional activity at the h5-HT_{2C} receptor in the range of 0 to 100%.

Preferred maximal functional activity at the h5-HT_{2C} receptor as described above are above 30%; especially preferred above 50%, particularly preferred above 60%. Most preferred maximal functional activity at the h5-HT_{2C} receptor are above 70%.

5 3. Regulation of feeding behaviour

The in vivo activity of compounds of formula (1) was assayed for ability to regulate feeding behaviour by assaying food consumption in food deprived animals as follows.

10 Test compounds are assessed following acute administration. Each study utilises a between-subjects design (typically n=8) and compares the effects of doses of the test agent to those of vehicle and a positive control.

15 The anorectic drug d-fenfluramine normally serves as a positive control. The route of drug administration, drug volume and injection-test-interval are dependent upon the compounds used. A palatable wet mash, made by adding powdered lab chow and water in a ration of 1:2 and mixing to a smooth consistency, is presented in 120 mL glass jars for 60 minutes each day. Intake is measured by weighing before and after each session. Care is taken to collect all spillage. Animals are allowed to habituate to the wet mash meal for 10 days. After drug administration, animals are allowed to consume the wet mash. Food consumption is assayed at pre-determined time points (typically, 1, 2 and 4 hours after administration). Food intake data are subjected to one-way analysis of variance (ANOVA) with drug as a between-subjects factor. A significant main effect is followed up by the performance of Dunnett's test in order to assess which treatment mean(s) are significantly different from the control mean. All statistical analyses were performed using Statistica Software, Version 5.0 (Statsoft Inc.) and Microsoft Excel 7.0 (Microsoft Corp.).

25

The thus determined activity of the Example indicated that the compounds maintain significant hypophagia 3 hours after a dose of 30 mg/kg per os.

Examples

Abbreviations:

PS-BEMP: 2-tert-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazo-
5 phosphorine on polystyrene

PS-NH₂: 4-(Aminomethyl)-polystyrene

TBME: tert-Butyl methyl ether

Starting materials:

10 4-chlorocarbonyl-piperazine-1-carboxylic acid tert-butyl ester was prepared following a modified procedure of document DE 25 50 111, Rhone-Poulenc.

Tetrabutylammonium hydrogencarbonate was prepared as described in St. C. Cheng, Ch. A. Blaine, M.G. Hill, K.R. Mann, Inorg. Chem. 35, 7704 (1996); C. Venturello, R. D'Aloisio, Synthesis 1985, 33.

15 N-Boc-piperazine is commercially available.

N-Fmoc-piperazine hydrobromide is commercially available.

4-(4-Fluorobenzyloxy)-benzyl alcohol is commercially available.

4-(4-Fluoro-benzyloxy)-phenyl-methanethiol was prepared in analogy to S. Vetter, Synth. Commun. 28, 3219 (1998).

20 cis-N-Boc-2,6-dimethylpiperazine was prepared as described in A. Muehlebach, P. Pino, Helv. Chim. Acta 73, 839 (1990).

Example 1

Piperazine-1-carboxylic acid 4-trifluoromethoxy-benzyl ester hydrochloride

Piperazine-1,4-dicarboxylic acid tert-butyl ester 4-trifluoromethoxy-benzyl ester: To a solution of 192 mg (1.0 mmol) 4-trifluoromethoxybenzyl alcohol in 5 ml acetonitrile are added 652 mg (1.5 mmol) PS-BEMP and 373 mg (1.5 mmol) 4-chlorocarbonyl-piperazine-1-carboxylic acid tert-butyl ester. The mixture is heated to reflux for 24h then cooled to rt, diluted with 5ml acetonitrile, 666 mg (4.5 mmol) PS-NH₂ added and shaken at rt for 16h. After filtration and evaporation the crude product is purified by flash chromatography on silica gel with hexane/AcOEt 50:50 : 180 mg colourless crystalline solid. ¹H-NMR (CDCl₃): 1.45 s, 9H, 3.35-3.55 m, 8H, 5.14 s, 2H, 7.20 d, 2H and 7.40 d, 2H, AB-system.

Piperazine-1-carboxylic acid 4-trifluoromethoxy-benzyl ester hydrochloride: A solution of 174 mg (0.49 mmol) piperazine-1,4-dicarboxylic acid tert-butyl ester 4-trifluoromethoxybenzyl ester in 4.9 ml 1.5M HCl/Et₂O and 0.98 ml abs. MeOH is stirred at rt for 3h. Evaporation of the reaction mixture provided 189 mg as colourless powder. ¹H-NMR (*d*₆-DMSO): 3.10 m, 4H and 3.62 m, 4H; 5.13 s, 2H; 7.40 d, 2H and 7.53 d, 2H, AB-system; 9.2 br, 2H. MS (ISP): 305.2 (M+H)⁺.

In analogy to Example 1 the following carbamates of Examples 2-24 can be prepared from the given starting material that is either commercially available or described in the literature:

Example 2

Piperazine-1-carboxylic acid 3,4-difluoro-benzyl ester hydrochloride was prepared from 3,4-difluorobenzyl alcohol; MS (ISP): 257.1 MH⁺.

Example 3

Piperazine-1-carboxylic acid 4-fluoro-benzyl ester hydrochloride was prepared from 4-fluorobenzyl alcohol; MS (ISP): 239.3 MH⁺.

Example 4

Piperazine-1-carboxylic acid 4-bromo-benzyl ester hydrochloride was prepared from 4-bromobenzyl alcohol; MS (ISP): 299.1 MH⁺.

5

Example 5

Piperazine-1-carboxylic acid 2-trifluoromethoxy-benzyl ester hydrochloride was prepared from 2-trifluoromethoxy-benzyl alcohol; MS (ISP): 305.2 MH⁺.

Example 6

10 Piperazine-1-carboxylic acid 2-chloro-5-nitro-benzyl ester hydrochloride was prepared from 2-chloro-5-nitro-benzyl alcohol; MS (ISP): 300.3 MH⁺.

Example 7

15 Piperazine-1-carboxylic acid 2-chloro-benzyl ester hydrochloride was prepared from 2-chlorobenzyl alcohol; MS (ISP): 255.1 MH⁺.

Example 8

Piperazine-1-carboxylic acid biphenyl-4-ylmethyl ester hydrochloride was prepared from 4-biphenylmethanol; MS (ISP): 297.3 MH⁺.

20

Example 9

Piperazine-1-carboxylic acid 3-methoxy-benzyl ester hydrochloride was prepared from 3-methoxybenzyl alcohol; MS (ISP): 250.2 MH⁺.

Example 10

Piperazine-1-carboxylic acid 3-trifluoromethyl-benzyl ester hydrochloride was prepared from 3-(trifluoromethyl)-benzyl alcohol; MS (ISP): 289.2 MH⁺.

5

Example 11

Piperazine-1-carboxylic acid 4-trifluoromethyl-benzyl ester hydrochloride was prepared from 4-(trifluoromethyl)-benzyl alcohol; MS (ISP): 289.1 MH⁺.

Example 12

- 10 Piperazine-1-carboxylic acid naphthalen-2-ylmethyl ester hydrochloride was prepared from 2-naphthalenemethanol; MS (ISP): 271.3 MH⁺.

Example 13

- 15 Piperazine-1-carboxylic acid naphthalen-1-ylmethyl ester hydrochloride was prepared from 1-naphthalenemethanol; MS (ISP): 271.3 MH⁺.

Example 14

Piperazine-1-carboxylic acid 2-methyl-benzyl ester hydrochloride was prepared from 2-methylbenzyl alcohol; MS (ISP): 235.4 MH⁺.

20

Example 15

Piperazine-1-carboxylic acid 2,4-dichloro-benzyl ester hydrochloride was prepared from 2,4-dichlorobenzyl alcohol; MS (EI): 288.0 M⁺.

Example 16

Piperazine-1-carboxylic acid 2,6-dichloro-benzyl ester hydrochloride was prepared from 2,6-dichlorobenzyl alcohol; MS (ISP): 289.1 MH⁺.

5

Example 17

Piperazine-1-carboxylic acid 4-tert-butyl-benzyl ester hydrochloride was prepared from 4-tert.-butyl-benzyl alcohol; MS (ISP): 277.3 MH⁺.

Example 18

10 Piperazine-1-carboxylic acid 2-fluoro-4-trifluoromethyl-benzyl ester hydrochloride was prepared from 2-fluoro-4-trifluoromethyl-benzyl alcohol; MS (ISP): 307.2 MH⁺.

Example 19

15 Piperazine-1-carboxylic acid 2,4-difluoro-benzyl ester hydrochloride was prepared from 2,4-difluorobenzyl alcohol; MS (ISP): 257.1 MH⁺.

Example 20

Piperazine-1-carboxylic acid 2-chloro-4-fluoro-benzyl ester hydrochloride was prepared from 2-chloro-4-fluorobenzyl alcohol; MS (ISP): 273.2 MH⁺.

20

Example 21

Piperazine-1-carboxylic acid 4-fluoro-2-trifluoromethyl-benzyl ester hydrochloride was prepared from 4-fluoro-2-trifluoromethyl-benzyl alcohol; MS (ISP): 307.3 MH⁺.

Example 22

Piperazine-1-carboxylic acid 4-difluoromethoxy-benzyl ester hydrochloride was prepared from 4-difluoromethoxy-benzyl alcohol; MS (ISP): 287.2 MH⁺.

5

Example 23

Piperazine-1-carboxylic acid 2,4-dimethyl-benzyl ester hydrochloride was prepared from 2,4-dimethyl-benzyl alcohol; MS (ISP): 248.2 MH⁺.

Example 24

- 10 Piperazine-1-carboxylic acid cyclohexylmethyl ester hydrochloride was prepared from hydroxymethyl-cyclohexane; MS (EI): 226.3 M⁺.

Example 25

Piperazine-1-carboxylic acid 2-fluoro-benzyl ester hydrochloride:

- 15 Piperazine-1,4-dicarboxylic acid tert-butyl ester 2-fluoro-benzyl ester: A solution of 4.47 g N-Boc-piperazine in 40 ml acetonitrile is saturated with dry carbon dioxide gas at rt. To this solution is added dropwise in 5 min. a solution of 8.50 g (28 mmol) terabutylammonium hydrogencarbonate (dried at 50°C at 0.1 mbar for 1h) in 30 ml acetonitrile, and then carbon dioxide gas bubbled into the stirred solution at rt for 1h.
- 20 Then 2.90 g (20 mmol) 2-fluorobenzyl chloride is added drop-wise within 5 min.. After stirring at rt for 3h the reaction mixture is evaporated, 150 ml of water added and extracted with AcOEt. The organic layer is washed with brine, dried over Na₂SO₄ and evaporated. Purification by flash chromatography on silica gel with hexane/AcOEt 50:50
- 25 provided 4.29 g piperazine-1,4-dicarboxylic acid tert-butyl ester 2-fluoro-benzyl ester as colourless powder. ¹H-NMR(CDCl₃): 1.46 s, 9H; 3.35 – 3.55 m, 8H; 5.21 s, 2H; 7.02 – 7.20 m, 2H and 7.27 – 7.45 m, 2H. MS (EI): 338.1 M⁺.

Piperazine-1-carboxylic acid 2-fluoro-benzyl ester hydrochloride: Prepared in analogy to Example 1. Colourless powder, $^1\text{H-NMR}$ (CDCl_3): 3.18 sbr, 4H and 3.85 sbr, 4H; 5.21 s, 2H; 7.03 – 7.22 m, 2H and 7.30 – 7.46 m, 2H; 10.1 br, 2H. MS (ISP): 239.3 ($\text{M}+\text{H}$) $^+$.

- 5 In analogy to Example 25 the following carbamates of Examples 26-31 can be prepared from the given starting material that is either commercially available or described in the literature:

Example 26

- 10 cis-2,6-Dimethyl-piperazine-1-carboxylic acid 4-chloro-benzyl ester hydrochloride

Prepared in analogy to Example 25 with cis-N-Boc-2,6-dimethyl-piperazine and 4-chloro-benzyl chloride. Colourless powder, $^1\text{H-NMR}$ ($d_6\text{-DMSO}$): 1.30 d 7.2 Hz, 6H; 3.0 – 3.25 m, 4H and 4.2 – 4.4m, 2H; 5.11 s, 2H; 7.35 – 7.55 AB-system, 4H; 9.5 br, 2H. MS (ISP): 283.1 ($\text{M}+\text{H}$) $^+$.

15

Example 27

cis-2,6-Dimethyl-piperazine-1-carboxylic acid 3-cyano-benzyl ester was prepared from 1-Boc-cis-3,5-dimethyl-piperazine and 3-cyano-benzyl bromide; MS (ISP): 274.3 MH^+ .

20

Example 28

cis-2,6-Dimethyl-piperazine-1-carboxylic acid 4-methoxycarbonyl-benzyl ester hydrochloride was prepared from 1-Boc-cis-3,5-dimethyl-piperazine and methyl 4-(bromomethyl)-benzoate; MS (ISP): 307.3 MH^+ .

Example 29

Piperazine-1-carboxylic acid 4-cyano-benzyl ester hydrochloride was prepared from 4-cyano-benzyl bromide; MS (ISP): 246.3 MH⁺.

5

Example 30

Piperazine-1-carboxylic acid 2-trifluoromethyl-benzyl ester hydrochloride was prepared from methanesulfonic acid 2-trifluoromethyl-benzyl ester that was prepared from 2-trifluoromethyl-benzyl alcohol and methanesulfonyl chloride following a text book procedure; MS (ISP): 289.2 MH⁺.

10

Example 31

Piperazine-1-carboxylic acid 4-chloro-2-fluoro-benzyl ester hydrochloride was prepared from 4-chloro-2-fluoro-benzyl bromide; ¹H-NMR (d₆-DMSO): 3.07 m, 4H and 3.59m, 4H, piperazine-H; 5.13 s, 2H, OCH₂; MS (ISP): 273.2 MH⁺.

15

Example 32

Piperazine-1-carbothioic acid S-(4-benzyloxy-benzyl) ester hydrochloride:

4-(4-Benzyloxy-benzylsulfanylcarbonyl)-piperazine-1-carboxylic acid tert-butyl ester:

20 Under argon 84 mg (1.5 mmol) of solid KOH are dissolved at rt in 214 mg (1 mmol) 4-(benzyloxy)-benzyl alcohol and 0.5 ml acetone. Then 76mg (1.1 mmol) carbon disulfide are added and the mixture thoroughly stirred for 2h. 323 mg (1.3 mmol) 4-chlorocarbonyl-piperazine-1-carboxylic acid tert-butyl ester are added and the mixture heated at rf for 8h. The reaction mixture is cooled to rt, 3ml of water added and extracted with TBME. The organic phase is washed with water and brine to pH 7, dried over Na₂SO₄
25 and evaporated. Purification of the crude product by preparative HPLC on a PRO C18 column with a H₂O/ MeCN gradient provided 87 mg 4-(4-benzyloxy-benzylsulfanylcarbonyl)-piperazine-1-carboxylic acid tert-butyl ester as colourless

powder. $^1\text{H-NMR}$ (CDCl_3): 1.46 s, 9H; 3.40 – 3.65 m, 8H; 4.13 s, 2H; 5.04 s, 2H; 6.90 d, 2H and 7.25 – 7.48 m, 7H.

5 Piperazine-1-carbothioic acid S-(4-benzyloxy-benzyl) ester hydrochloride: A solution of 86 mg (0.19 mmol) 4-(4-benzyloxy-benzylsulfanylcabonyl)-piperazine-1-carboxylic acid tert-butyl ester in 2.2 ml 1.5M HCl/Et₂O and 0.45 ml abs. MeOH is stirred at rt for 4h. Evaporation of the reaction mixture provided 64 mg product as colourless powder. $^1\text{H-NMR}$ (d_6 -DMSO): 3.03 – 3.17 m, 4H and 3.58 – 3.73 m, 4H; 4.09 s, 2H; 5.08 s, 2H; 6.95 d, J = 7.5 Hz, 2H and 7.26 d, J = 7.5 Hz, 2H (AB-system) and 7.30 – 7.50 m, 5H; 9.2 br, 2H.
10 MS (ISP): 343.2 (M+H)⁺.

In analogy to Example 32 the following thiocarbamates of Examples 33-39 can be prepared from the given starting material that is either commercially available or described in the literature:

15

Example 33

Piperazine-1-carbothioic acid S-(4-bromo-benzyl) ester hydrochloride was prepared from 4-bromobenzyl alcohol; $^1\text{H-NMR}$ (d_6 -DMSO): 3.10 m, 4H and 3.68 m, 4H, piperazine-H; 4.12 s, 2H, SCH₂; MS (ISP): 317.1 MH⁺.

20

Example 34

Piperazine-1-carbothioic acid S-(4-trifluoromethoxy-benzyl) ester hydrochloride was prepared from 4-trifluoromethoxy-benzyl alcohol; $^1\text{H-NMR}$ (d_6 -DMSO): 3.12 m, 4H and 3.70 m, 4H, piperazine-H; 4.21 s, 2H, SCH₂; MS (ISP): 321.3 MH⁺.

25

Example 35

Piperazine-1-carbothioic acid S-(4-fluoro-benzyl) ester hydrochloride was prepared from 4-fluoro-benzyl alcohol; $^1\text{H-NMR}$ (d_6 -DMSO): 3.10 m, 4H and 3.68 m, 4H, piperazine-H; 4.14 s, 2H, SCH_2 ; MS (ISP): 255.1 MH^+ .

5

Example 36

Piperazine-1-carbothioic acid S-(2,4-difluoro-benzyl) ester hydrochloride was prepared from 2,4-difluoro -benzyl alcohol; $^1\text{H-NMR}$ (d_6 -DMSO): 3.10 m, 4H and 3.68 m, 4H, piperazine-H; 4.14 s, 2H, SCH_2 ; MS (ISP): 273.2 MH^+ .

10

Example 37

Piperazine-1-carbothioic acid S-(4-methoxy-benzyl) ester hydrochloride was prepared from 4-methoxy-benzyl alcohol; $^1\text{H-NMR}$ (d_6 -DMSO): 3.10 m, 4H and 3.67 m, 4H, piperazine-H; 3.72 s, 3H, OCH_3 ; 4.09 s, 2H, SCH_2 ; MS (ISP): 267.3 MH^+ .

15

Example 38

Piperazine-1-carbothioic acid S-(2,4-dimethyl-benzyl) ester hydrochloride was prepared from 2,4-dimethylbenzyl alcohol; $^1\text{H-NMR}$ (d_6 -DMSO): 2.23 s, 3H and 2.27 s, 3H, 2 x CH_3 -aryl; 3.10 m, 4H and 3.66 m, 4H, piperazine-H; 4.10 s, 2H, SCH_2 ; MS (ISP): 265.3 MH^+ .

20

Example 39

Piperazine-1-carbothioic acid S-(2-fluoro-4-trifluoromethyl-benzyl) ester hydrochloride was prepared from 2-fluoro-4-trifluoromethyl-benzyl alcohol; $^1\text{H-NMR}$ (d_6 -DMSO): 3.10 m, 4H and 3.67 m, 4H, piperazine-H; 4.24 s, 2H, SCH_2 ; MS (ISP): 323.3 MH^+ .

25

Example 40

Piperazine-1-carbothioic acid S-[4-(4-fluoro-benzyloxy)-benzyl] ester hydrochloride:

4-(4-Fluoro-benzyloxy)-phenyl-methanethiol in analogy to S. Vetter, Synth. Commun. 28, 3219 (1998): A mixture of 6.00 (26 mmol) 4-(4-fluorobenzyloxy)-benzyl alcohol and 3.93 g (52 mmol) thiourea is dissolved at 50°C in water/acetone 1:1.5. To this solution 7.75 ml 5N HCl are added dropwise and the mixture stirred at 50°C for 16h. Then the solution is cooled and extracted quickly twice with Et₂O, the aqueous layer made alkaline by addition of 3.1 g (78 mmol) NaOH pellets and heated to rf for 3h. Acidification of the reaction mixture at rt with 5N HCl, extraction with AcOEt, drying with Na₂SO₄ and evaporation furnished 6.25 g 4-(4-fluoro-benzyloxy)-phenyl-methanethiol as a colourless powder: mp. 77-80°C. ¹H-NMR (d₆-DMSO): 2.77 t, J = 7.5 Hz, 1H; 3.68 d, J = 7.5 Hz, 2H; 5.06 s, 2H; 6.94 d, 2H and 7.18 – 7.32 m, 4H and 7.45 – 7.58 m, 2H.

4-[4-(4-Fluoro-benzyloxy)-benzylsulfanylcarbonyl]-piperazine-1-carboxylic acid tert-butyl ester: 5.84 g (23.5 mmol) 4-chlorocarbonyl-piperazine-1-carboxylic acid tert-butyl ester are added to a solution of 6.0 g (24.2 mmol) 4-(4-fluoro-benzyloxy)-phenyl-methanethiol in 14.6 ml pyridine. The solution was heated to 100°C for 3.5h, then cooled to rt, 10 ml of water added and the volume reduced to a third. The resulting precipitate is collected, washed with water and dried. The crude product is re-crystallized from hexane/AcOEt. Flash chromatography on silica gel provided 4.90 g 4-[4-(4-fluoro-benzyloxy)-benzylsulfanylcarbonyl]-piperazine-1-carboxylic acid tert-butyl ester as colourless powder, mp: 123-124°C. ¹H-NMR (CDCl₃): 1.46 s, 9H; 3.38 – 3.60 m, 8H; 4.13 s, 2H; 5.00 s, 2H; 6.89 d, 2H, 7.06 t, 2H, 7.28 d, 2H and 7.40 dd, 2H.

Piperazine-1-carbothioic acid S-[4-(4-fluoro-benzyloxy)-benzyl] ester hydrochloride: A solution of 4.89 g (10.6 mmol) 4-[4-(4-fluoro-benzyloxy)-benzylsulfanylcarbonyl]-piperazine-1-carboxylic acid tert-butyl ester in 120.6 ml 1.5M HCl/Et₂O and 24.1 ml abs. MeOH was stirred at rt for 6h. Evaporation of the reaction mixture provided 3.96 g piperazine-1-carbothioic acid S-[4-(4-fluoro-benzyloxy)-benzyl] ester hydrochloride as colourless powder, mp. 169-169.5°C. ¹H-NMR(d₆-DMSO): 3.05 m, 4H and 3.58 – 3.75 m,

4H; 4.09 s, 2H; 5.06 s, 2H; 6.94 d, 2H, 7.17 – 7.30 m, 4H and 7.43 – 7.55 m, 2H; 9.2 br, 2H.
MS (ISP): 361.2 (M+H)⁺.

Beispiel 41

5 Piperazine-1-carboxylic acid 4-benzyloxy-benzyl ester:

(RS)-Carbonic acid 4-benzyloxy-benzyl ester 1-chloro-ethyl ester: A solution of 1.07 g (5.0 mmol) 4-benzyloxybenzyl alcohol and 0.786 g (5.5 mmol) 1-chloroethyl chloroformate in 25 ml CH₂Cl₂ is cooled to 0°C and 0.435 g (5.5 mmol) pyridine added. After stirring at rt for 2h the reaction mixture is quenched with 1N HCl, the organic phase separated and
10 washed with sat. NaHCO₃ solution and brine, dried over Na₂SO₄ and evaporated: 1.58 g (98%) (RS)-carbonic acid 4-benzyloxy-benzyl ester 1-chloro-ethyl ester as light yellow oil.
¹H-NMR (CDCl₃): 1.81 d, J = 6 Hz, 3H; 5.07 s, 2H; 5.14 and 5.17, AB-system J = 15 Hz, 2H; 6.43 q, J = 6 Hz, 1H; 6.97 d, J = 8.5 Hz, 2H and 7.30 – 7.45 m, 7H.

15 Piperazine-1,4-dicarboxylic acid 4-benzyloxy-benzyl ester 9H-fluoren-9-ylmethyl ester: To a solution of 1.51 g (4.7 mmol) (RS)-carbonic acid 4-benzyloxy-benzyl ester 1-chloro-ethyl ester in 57 ml of CH₂Cl₂ is added dropwise a solution of 1.47 g (4.7 mmol) N-Fmoc-piperazine (obtained from N-Fmoc-piperazine hydrobromide by treatment with aqueous NaHCO₃ and extraction with TBME, drying the organic layer over Na₂SO₄ and
20 evaporation under reduced pressure at < 30°C) in 18 ml CH₂Cl₂ at 0°C. The reaction is slightly exothermic and a colourless precipitate is formed. After 1h at 0°C the mixture is allowed to warm to rt and stirred for further 62 h. Then the reaction is quenched with 2.35 ml 4M K₂CO₃, filtered over a plug of Na₂SO₄ and evaporated. The crude product (2.67 g) is purified by flash-chromatography on silica gel with hexane/AcOEt 50:50 as eluent: 1.54 g
25 (60%) RO-72-0160/000 as yellow solid. IR (Nujol): 1699 cm⁻¹. ¹H-NMR (CDCl₃): 3.25 – 3.60 br, 8H; 4.23 t, J = 6.4 Hz, 1H; 4.48 d, J = 6.4 Hz, 2H; 5.06 s and 5.07 s, 4H; 6.97 d, J = 8.4 Hz, 2H, 7.26 – 7.45, m 11H, 7.55 d, J = 7.6 Hz, 2H and 7.76 d, J = 7.6 Hz, 2H. MS (ISP): 566.4 (M+NH₄)⁺; 571.4 (M+Na)⁺.

30 Piperazine-1-carboxylic acid 4-benzyloxy-benzyl ester: A solution of 274 mg (0.5 mmol) piperazine-1,4-dicarboxylic acid 4-benzyloxy-benzyl ester 9H-fluoren-9-ylmethyl ester in 13 ml morpholine is stirred at rt for 1h. Then 23 ml of chilled water is added, the suspension filtered and the filtrate extracted with TBME. The organic layer is washed with

water, brine, dried over Na_2SO_4 and evaporated: 54 mg piperazine-1-carboxylic acid 4-benzyloxy-benzyl ester as light yellow, waxy solid. MIR: 3300 cm^{-1} , 1688 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 1.77 br, 1H; 2.75 – 2.90 m, 4H and 3.40 – 3.50 m, 4H; 5.06 s and 5.07 s, 4H; 6.96 d, $J = 8.8\text{ Hz}$, 2H and 7.28 – 7.44 m, 7H. MS (ISP): 327.3 (M+H)^+ .

5

In analogy to Example 41 the following carbamates of Examples 42-45 can be prepared from the given starting material that is either commercially available or described in the literature.

Example 42

10 Piperazine-1-carboxylic acid 4-(4-fluoro-benzyloxy)-benzyl ester

(RS)-Carbonic acid 1-chloro-ethyl ester 4-(4-fluoro-benzyloxy)-benzyl ester: Prepared in analogy to (RS)-carbonic acid 4-benzyloxy-benzyl ester 1-chloro-ethyl ester (Example 41) from 4-(4-fluoro-benzyloxy)-benzyl alcohol and 1-chloroethyl chloroformate: light yellow oil. $^1\text{H-NMR}$ (CDCl_3): 1.81 d, $J = 5.5\text{ Hz}$, 3H; 5.03 s, 2H; 5.13 and 5.18 J = 5.5 Hz, AB-system, 2H; 6.43 q, 1H; 6.95 d, $J = 8.4\text{ Hz}$, 2H, 7.07 t $J = 8.4\text{ Hz}$, 2H, 7.28 – 7.45 m, 4H.

15

Piperazine-1,4-dicarboxylic acid 9H-fluoren-9-ylmethyl ester 4-(4-fluoro-benzyloxy)-benzyl ester: Prepared in analogy to piperazine-1,4-dicarboxylic acid 4-benzyloxy-benzyl ester 9H-fluoren-9-ylmethyl ester (Example 41) from (RS)-carbonic acid 1-chloro-ethyl ester 4-(4-fluoro-benzyloxy)-benzyl ester) and N-Fmoc-piperazine: yellow solid. $^1\text{H-NMR}$ (CDCl_3): 3.3 – 3.6 m, 8H; 4.23 t, $J = 6\text{ Hz}$, 1 H; 4.48 d, $J = 6\text{ Hz}$, 2H; 5.03 s, 2H; 5.08 s, 2H; 6.95 d, $J = 8.5\text{ Hz}$, 2H, 7.08 t, $J = 8.5\text{ Hz}$, 2H, 7.25 – 7.46 m, 8H, 7.55 d, $J = 7\text{ Hz}$, 2H and 7.77 d, $J = 7\text{ Hz}$, 2H.

20

25 Piperazine-1-carboxylic acid 4-(4-fluoro-benzyloxy)-benzyl ester: Prepared in analogy to piperazine-1-carboxylic acid 4-benzyloxy-benzyl ester (Example 41) from piperazine-1,4-dicarboxylic acid 9H-fluoren-9-ylmethyl ester 4-(4-fluoro-benzyloxy)-benzyl ester and morpholine: colourless, waxy solid: IR (Nujol): 3341 cm^{-1} , 1689 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 1.75 br, 1H; 2.85 – 2.90 m, 4H and 3.40 – 3.55 m, 4H; 5.02 s, 2H; 5.07 s, 2H; 6.94 d, $J = 8.4\text{ Hz}$, 2H, 7.07 t, $J = 8.8\text{ Hz}$, 2H, 7.30 d, $J = 8.4\text{ Hz}$, 2H and 7.38 – 7.42 m, 2H. MS (EI): 344.3 M^+ .

30

Example 43

Piperazine-1-carboxylic acid 4-methoxy-benzyl ester hydrochloride was prepared from 4-methoxy-benzyl alcohol via the following intermediates:

- 5 (RS)-Carbonic acid 1-chloro-ethyl ester 4-methoxy-benzyl ester: $^1\text{H-NMR}$ (CDCl_3): 1.81 d, $J = 8.2$ Hz, 3H; 3.81 s, 3H; 5.14 and 5.18 AB-system, $J = 16$ Hz, 2H; 6.42 q, $J = 8.2$ Hz, 1H; 6.90 d, $J = 8$ Hz, 2H and 7.36 d, $J = 8$ Hz, 2H. MS (EI): 244.1 M^+ .

- Piperazine-1,4-dicarboxylic acid 9H-fluoren-9-ylmethyl ester 4-methoxy-benzyl ester: $^1\text{H-NMR}$ (CDCl_3): 3.32-3.58 br, 8H; 3.81 s, 3H; 4.24 t, $J = 6$ Hz, 1H; 4.58 d, $J = 6$ Hz, 2H; 5.07
10 s, 2H; 6.92 d, $J = 8$ Hz, 2H, 7.54 - 7.46 m, 6H, 7.54 d, $J = 8$ Hz, 2H, 7.78 d, $J = 8$ Hz, 2H.

- Piperazine-1-carboxylic acid 4-methoxy-benzyl ester hydrochloride: Deprotection with morpholine lead to piperazine-1-carboxylic acid 4-methoxy-benzyl ester. The hydrochloride was prepared by addition of HCl/ Et_2O to a solution of the free base in Et_2O followed by evaporation. $^1\text{H-NMR}$ (d_6 -DMSO): 3.10 m, 4H and 3.60 m, 4H, piperazine-H;
15 5.02 s, 2H. MS (ISP): 251.2 MH^+ .

Example 44

Piperazine-1-carboxylic acid benzhydryl ester was prepared from diphenyl carbinol via the following intermediates:

- 20 (RS)-Carbonic acid benzhydryl ester 1-chloro-ethyl ester: $^1\text{H-NMR}$ (CDCl_3): 1.83 d, $J = 5.8$ Hz, 3H; 6.41 q, $J = 5.8$ Hz, 1H; 6.75 s, 1H; 7.25 - 7.43 m, 10H.

Piperazine-1,4-dicarboxylic acid benzhydryl ester 9H-fluoren-9-ylmethyl ester: $^1\text{H-NMR}$ (CDCl_3): 3.32-3.68 br, 8H; 4.24 t, $J = 6$ Hz, 1H; 4.48 d, $J = 6$ Hz, 2H; 6.82 s, 1H; 7.25-7.44 m, 14H and 7.56 d, $J = 8$ Hz, 2H and 7.78 d, $J = 8$ Hz, 2H.

- 25 Piperazine-1-carboxylic acid benzhydryl ester: $^1\text{H-NMR}$ (CDCl_3): 1.70 br, 1H; 2.80- 2.85 m, 4H and 3.40-3.70 m, 4H, piperazine-H; 6.82 s, 1H; 7.25-7.35 m, 10H. MS (ISP): 297.3 MH^+ .

Example 45

(RS)-Piperazine-1-carboxylic acid 1-phenyl-ethyl ester was prepared from (RS)-1-phenylethanol via the following intermediates:

(RS)-Carbonic acid 1-chloro-ethyl ester 1-phenyl-ethyl ester: $^1\text{H-NMR}$ (CDCl_3): 1.62 d, $J = 6.5$ Hz and 1.64 d, $J = 6.5$ Hz, 3H; 1.79 d, $J = 5.8$ Hz and 1.64 d, $J = 5.8$ Hz, 3H; 5.77 q, $J = 6.5$ Hz and 5.80 q, $J = 6.5$ Hz, 1H; 6.37 q, $J = 5.8$ Hz and 6.41 q, $J = 5.8$ Hz, 1H; 7.37 m, 5H.

(RS)-Piperazine-1,4-dicarboxylic acid 9H-fluoren-9-ylmethyl ester 1-phenyl-ethyl ester: $^1\text{H-NMR}$ (CDCl_3): 1.56 d, $J = 6.5$ Hz, 3H; 3.32-3.58 br, 8H; 4.24 t, $J = 6$ Hz, 1H; 4.68 d, $J = 6$ Hz, 2H; 5.83 d, $J = 6.5$ Hz, 1H; 7.25-7.44 m, 9H and 7.56 d, $J = 8$ Hz, 2H and 7.78 d, $J = 8$ Hz, 2H.

(RS)-Piperazine-1-carboxylic acid 1-phenyl-ethyl ester: $^1\text{H-NMR}$ (CDCl_3): 1.54 d, $J = 4$ Hz, 3H; 1.68 br, 1H; 2.75- 2.85 m, 4H and 3.40-3.55 m, 4H, piperazine-H; 5.82 q, $J = 4$ Hz, 1H; 7.25-7.38 m, 5H. MS (EI): 234.2 M^+ .

15

Example 46

Piperazine-1-carboxylic acid phenethyl ester:

To a solution of 4-chlorocarbonyl-piperazine-1-carboxylic acid tert-butyl ester in dichloromethane (30 vol.) was added phenethyl alcohol (2 eq), triethylamine (3 eq) and pyridine (1 eq) and the mixture was shaken at 25°C for 6 days. The mixture was evaporated, and the resultant crude material purified by preparative HPLC [C18, 10 mM aqueous NH_4OAc solution:MeOH] to afford the intermediate product, which was used immediately in the next step.

To a solution of the above intermediate in methanol (50 volumes) was added a solution of HCl in dioxane (4 M, 10 eq) and the mixture was shaken for 16 h. Evaporation to dryness afforded the desired product.

$^1\text{H-NMR}$ (400 MHz, d_6 -DMSO): 2.90 (2H, t, $J = 6.5$ Hz), 2.99-3.06 (4H, m), 3.52-3.59 (4H, m), 4.22 (2H, t, $J = 6.5$ Hz), 7.19-7.34 (5H, m) and 9.29-9.43 (2H, br s); HPLC:

[XTERRA; methanol-10mM aqueous NH_4OAc (40:60); 2mL/min; 210 nm] 100% (0.98 min).

Example 47

5 cis-2,6-Dimethylpiperazine-1-carboxylic acid 5-[2-(3-chlorobenzyloxy)]pyridyl-methyl ester fumarate:

cis-2,6-Dimethylpiperazine-1,4-dicarboxylic acid 5-(2-chloropyridyl)-methyl ester tert-butyl ester: A solution of 2-chloro-5-(hydroxymethyl)pyridine (2.6 g, 18 mmol), 1-tert-butoxycarbonyl-2,6-dimethyl-4-chlorocarbonylpiperazine (3.8 g, 14 mmol), pyridine (1.5
10 mL, 19 mmol) and triethylamine (7.6 mL, 52 mmol) in dichloromethane (100 mL) was stirred for 96 h. The mixture was concentrated in vacuo then partitioned between water (100 mL) and ethyl acetate (3 x 50 mL). The combined organic extracts were washed with water and brine, then dried over sodium sulfate, concentrated in vacuo and purified by flash column chromatography [SiO_2 ; isohexane – ethyl acetate (4:1)] to give the product as
15 a white solid (1.7 g, 32%), m.p. 75-76°C. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 8.40 (1H, d, J = 2.5 Hz), 7.67 (1H, dd, J = 2.5, 8 Hz), 7.33 (1H, d, J = 8 Hz), 5.14 (2H, s), 4.23-4.14 (2H, m), 4.04-3.82 (2H, m), 3.04-2.86 (2H, m), 1.47 (9H, s) and 1.23 (6H, d, J = 7 Hz).

cis-2,6-Dimethylpiperazine-1,4-dicarboxylic acid 5-[2-(3-chlorobenzyloxy)]pyridyl-
20 methyl ester tert-butyl ester: To a stirred mixture of cis-2,6-Dimethylpiperazine-1,4-dicarboxylic acid 5-(2-chloropyridyl)methyl ester tert-butyl ester (0.25 g, 0.7 mmol), 3-chlorobenzyl alcohol (0.14 g, 1.0 mmol), potassium carbonate (0.09 g, 0.7 mmol) and powdered potassium hydroxide (85%, 0.17 g, 2.6 mmol) in toluene (10 mL) was added tris-[2-(2-methoxyethoxy)ethyl]amine (0.02 g, 0.007 mmol). The mixture was heated to
25 120°C, stirred for 4 h, cooled to room temperature, poured into water (20 mL) and extracted with ether (3 x 30 mL). The combined organic extracts were washed with water and brine, then dried over sodium sulfate, concentrated in vacuo and purified by flash column chromatography [SiO_2 ; isohexane – ethyl acetate (9:1) to (3:1)] to give the product as a viscous oil (0.13 g, 40%). $^1\text{H-NMR}$ (400 MHz, CDCl_3): 8.16 (1H, d, J = 2.5 Hz), 7.63
30 (1H, dd, J = 2.5, 8.5 Hz), 7.45 (1H, s), 7.34-7.27 (3H, m), 6.81 (1H, d, J = 8.5 Hz), 5.36 (2H, s), 5.08 (2H, s), 4.22-4.14 (2H, m), 4.05-3.80 (2H, m), 3.08-2.84 (2H, m), 1.47 (9H, s)

and 1.22 (6H, d, J = 7 Hz); HPLC [Xterra, 2.0 mL/min; methanol-10 mM aqueous ammonium acetate solution (50:50) to (80:20) over 5 min then (80:20)] 97% (7.81 min).

5 cis-2,6-Dimethylpiperazine-1-carboxylic acid 5-[2-(3-chlorobenzoyloxy)]pyridyl-methyl ester fumarate: To a stirred solution of cis-2,6-Dimethylpiperazine-1,4-dicarboxylic acid 5-[2-(3-chlorobenzoyloxy)]pyridyl-methyl ester tert-butyl ester (0.12 g, 0.24 mmol) in methanol (5 mL) was added drop-wise a solution of hydrogen chloride in dioxan (4 M, 0.61 mL, 2.4 mmol). The mixture was stirred for 18 h then concentrated in vacuo. The residue was partitioned between ether (2 x 10 mL) and aqueous sodium hydroxide
10 solution (2 M, 10 mL). The combined organic layers were washed with water and brine then dried over sodium sulfate, concentrated in vacuo, dissolved in warm 2-propanol (1 mL) and added drop-wise to a stirred solution of fumaric acid (0.033 g, 0.28 mmol) in warm 2-propanol (1 mL). The mixture was cooled to 0°C, stirred for 30 min then filtered. The filter-cake was washed with 2-propanol and ether then dried in vacuo to give the
15 product as a white solid (0.071 g, 57%), m.p. 172°C (dec.). ¹H-NMR (400 MHz, *d*₆-DMSO): 8.18 (1H, d, J = 2.5 Hz), 7.76 (1H, dd, J = 2.5, 8.5 Hz), 7.50 (1H, s), 7.42-7.36 (3H, m), 6.93 (1H, d, J = 8.5 Hz), 6.59 (2H, s), 5.37 (2H, s), 5.04 (2H, s), 4.01-3.93 (2H, m), 2.77 (2H, d, J = 12 Hz), 2.70 (2H, dd, J 4, 12 Hz) and 1.18 (6H, d, J = 7 Hz).

20

Example 48

Piperazine-1-carboxylic acid 5-[2-(3-chlorobenzoyloxy)]pyridyl-methyl ester fumarate:

6-(3-Chlorobenzoyloxy)nicotinic acid: To a stirred suspension of sodium hydride (60%, 0.76 g, 19 mmol) in toluene (10 mL) was added portion-wise over 30 min 6-chloronicotinic acid (1.0 g, 6.3 mmol). The mixture was stirred for 30 min then cooled to
25 0°C. A solution of 3-chloro-benzyl alcohol (0.69 g, 6.4 mmol) in toluene (5 mL) was added drop-wise over 10 min. The mixture was warmed to room temperature, DMF (20 mL) was added and the mixture was heated to 95°C and stirred for 18 h. The mixture was cooled to room temperature then poured into water (30 mL). The aqueous mixture was acidified to pH 2 and extracted with ethyl acetate (2 x 30 mL). The combined organic
30 extracts were washed with water and brine, then dried over sodium sulfate and concentrated in vacuo to give a yellow solid (2.36 g). The residue was re-crystallised [2-

propanol-water, (2:1)] to give the product as a white solid (0.85 g, 51%), m.p. 158°C (dec.). ¹H-NMR (400 MHz, CDCl₃): 8.93 (1H, d, J = 2.5 Hz), 8.24 (1H, dd, J = 2.5, 8.5 Hz), 7.46 (1H, s), 7.35-7.29 (3H, m), 6.87 (1H, dd, J = 1, 8.5 Hz) and 5.45 (2H, s).

5 2-(3-Chlorobenzyloxy)-5-(hydroxymethyl)pyridine: To a stirred suspension of lithium aluminium hydride (0.14 g, 3.7 mmol) in THF (10 mL) at 0°C under Ar was added portion-wise 6-(3-chlorobenzyloxy)nicotinic acid (0.60 g, 2.3 mmol). The mixture was warmed to room temperature, stirred for 2 h then cooled to 0°C. Saturated aqueous sodium potassium tartrate solution (1 mL) was added drop-wise followed by sodium
10 sulfate decahydrate (2 g). The mixture was diluted with ether (30 mL), stirred for 1 h then filtered through kieselguhr. The filter-cake was washed with ether (10 mL); the combined filtrates were concentrated in vacuo and purified by flash column chromatography [isohexane – ethyl acetate (4:1) to (1:1)] to give the product as a viscous oil (0.25 g, 44%). ¹H-NMR (400 MHz, CDCl₃): 8.11 (1H, d, J = 2.5 Hz), 7.63 (1H, dd, J = 2.5, 8.5 Hz), 7.45
15 (1H, s), 7.33-7.25 (3H, m), 6.82 (1H, d, J = 8.5 Hz), 5.35 (2H, s), 4.62 (2H, d, J = 4 Hz) and 1.87 (1H, t, J = 4 Hz, -OH). HPLC: [Xterra, 2.0 mL/min; methanol-10 mM aqueous ammonium acetate solution (50:50) to (80:20) over 5 min then (80:20)] 98% (3.95 min).

Piperazine-1,4-dicarboxylic acid 5-[2-(3-chlorobenzyloxy)]pyridyl-methyl ester tert-butyl
20 ester: To a stirred suspension of sodium hydride (60%, 0.042 g, 1.1 mmol) in DMF (2 mL) was added drop-wise a solution of 2-(3-chlorobenzyloxy)-5-(hydroxymethyl)pyridine (0.22 g, 0.9 mmol) in DMF (1 mL). The mixture was stirred for 30 min then a solution of 1-tert-butoxycarbonyl-4-chlorocarbonylpiperazine (0.22 g, 0.9 mmol) in DMF (1 mL) was added. The mixture was stirred for 18 h then poured into water (10 mL) and extracted
25 with ether (2 x 10 mL). The combined organic extracts were washed with water and brine, then dried over sodium sulfate, concentrated in vacuo and purified by flash column chromatography [SiO₂; isohexane – ethyl acetate (9:1) to (3:1)] to give the product as a viscous oil (0.17 g, 41%). ¹H-NMR (400 MHz, CDCl₃): 8.16 (1H, d, J = 2.5 Hz), 7.63 (1H, dd, J = 2.5, 8.5 Hz), 7.45 (1H, s), 7.34-7.26 (3H, m), 6.81 (1H, d, J = 8.5 Hz), 5.36 (2H, s),
30 5.08 (2H, s), 3.48-3.36 (8H, m) and 1.46 (9H, s). HPLC: [Xterra, 2.0 mL/min; methanol-10 mM aqueous ammonium acetate solution (50:50) to (80:20) over 5 min then (80:20)] 97% (7.35 min).

Piperazine-1-carboxylic acid 5-[2-(3-chlorobenzyloxy)]pyridyl-methyl ester fumarate: To a stirred solution of Piperazine-1,4-dicarboxylic acid 5-[2-(3-chlorobenzyloxy)]pyridyl-methyl ester tert-butyl ester (0.16 g, 0.35 mmol) in methanol (5 mL) was added drop-wise
5 a solution of hydrogen chloride in dioxan (4 M, 0.9 mL, 3.6 mmol). The mixture was stirred for 18 h then concentrated in vacuo. The residue was partitioned between ether (2 x 10 mL) and aqueous sodium hydroxide solution (2 M, 10 mL). The combined organic layers were washed with water and brine then dried over sodium sulfate, concentrated in vacuo, dissolved in warm 2-propanol (2 mL) and added drop-wise to a stirred solution of
10 fumaric acid (0.047 g, 0.41 mmol) in warm 2-propanol (2 mL). The mixture was cooled to 0°C, stirred for 30 min then filtered. The filter-cake was washed with 2-propanol and ether then dried in vacuo to give the product as a white solid (0.089 g, 54%), m.p. 148°C (dec.).
¹H-NMR (400 MHz, *d*₆-DMSO): 8.19 (1H, d, *J* = 2.5 Hz), 7.77 (1H, dd, *J* = 2.5, 8.5 Hz), 7.50 (1H, s), 7.42-7.36 (3H, m), 6.92 (1H, d, *J* = 8.5 Hz), 6.52 (2H, s), 5.36 (2H, s), 5.04
15 (2H, s), 3.45-3.40 (4H, m) and 2.86-2.80 (4H, m).

Example 49

cis-2,6-Dimethylpiperazine-1-carboxylic acid 2-(2-thienyl)ethyl ester:

To a solution of cis-4-chlorocarbonyl-2,6-dimethyl-piperazine-1-carboxylic acid tert-butyl
20 ester in dichloromethane (30 vol.) was added 2-(2-thienyl)ethanol (2 eq), triethylamine (3 eq) and pyridine (1 eq) and the mixture was shaken at 25 °C for 6 days. The mixture was evaporated, and the resultant crude material purified by preparative HPLC [C18, 10 mM aqueous NH₄OAc solution:MeOH] to afford the intermediate product, which was used immediately in the next step.

25 To a solution of the above intermediate in methanol (50 volumes) was added a solution of HCl in dioxane (4 M, 10 eq) and the mixture was shaken for 16 h. Evaporation to dryness afforded the desired product. HPLC: [XTERRA; methanol-10mM aqueous NH₄OAc (60:40); 2 mL/min; 210 nm] 94.5% (0.83 min); MS(ISP): 269 MH⁺.

30 cis-4-chlorocarbonyl-2,6-dimethyl-piperazine-1-carboxylic acid tert-butyl ester was prepared in analogy to 4-chlorocarbonyl-piperazine-1-carboxylic acid tert-butyl ester from cis-2,6-dimethylpiperazine-1-carboxylic acid tert-butyl ester (A. Muehlebach, P.

Pino, *Helv. Chim. Acta* 73, 839 (1990)) by a modified procedure of Rhone-Poulenc DE 25 50 111 (Rhone-Poulenc).

Example 50

5 cis-2,6-Dimethylpiperazine-1-carboxylic acid 2-fluoro-benzyl ester:

To a solution of cis-4-chlorocarbonyl-2,6-dimethyl-piperazine-1-carboxylic acid tert-butyl ester in dichloromethane (30 vol.) was added 2-fluorobenzyl alcohol (2 eq), triethylamine (3 eq) and pyridine (1 eq) and the mixture was shaken at 25 °C for 6 days. The mixture was evaporated, and the resultant crude material purified by preparative HPLC [C18, 10
10 mM aqueous NH₄OAc solution:MeOH] to afford the intermediate product, which was used immediately in the next step.

To a solution of the above intermediate in methanol (50 volumes) was added a solution of HCl in dioxane (4 M, 10 eq) and the mixture was shaken for 16 h. Evaporation to dryness afforded the desired product. HPLC: [XTERRA; methanol-10 mM aqueous NH₄OAc
15 (60:40); 2 mL/min; 210 nm] 96.8% (0.88 min); MS (ISP): 267 MH⁺.

cis-4-chlorocarbonyl-2,6-dimethyl-piperazine-1-carboxylic acid tert-butyl ester was prepared in analogy to 4-chlorocarbonyl-piperazine-1-carboxylic acid tert-butyl ester from cis-2,6-dimethylpiperazine-1-carboxylic acid tert-butyl ester (A. Muehlebach, P. Pino, *Helv. Chim. Acta* 73, 839 (1990)) by a modified procedure of Rhone-Poulenc DE 25
20 50 111 (Rhone-Poulenc).

Example 51

Piperazine-1-carbothioic acid S-[4-(3-nitrobenzyl)oxy]benzyl ester

[(4-tert-Butyl-dimethylsilyloxy)benzylsulfanylcarbonyl]-piperazine-4-carboxylic acid tert-
25 butyl ester: To a stirred mixture of 4-(tert-butyldimethylsilyloxy)benzyl mercaptan (Bioorg. Med. Chem. Letts. 7, 1013-1023 (1999)) (0.74 g, 2.9 mmol), triethylamine (0.8 mL, 5.8 mmol), 4-dimethylaminopyridine (0.05 g) and THF (10 mL) at 0°C under Ar was added portion-wise over 10 minutes 4-chlorocarbonyl-piperazine-1-carboxylic acid tert-butyl ester (0.65 g, 2.6 mmol). The mixture was warmed to room temperature and stirred
30 for 1 h then heated to 50°C and stirred for 3 h. The mixture was cooled to room

temperature and partitioned between ethyl acetate (2 x 30 mL) and water (50 mL). The combined organic extracts were washed with water, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography [SiO₂; isohexane, ethyl acetate (9:1)] to give the product as a clear oil, which solidified on
5 standing (0.75 g, 56%): m.p. 53 - 54°C. ¹H-NMR (400 MHz, CDCl₃): 0.18 (6H, s), 0.96 (9H, s), 1.46 (9H, s), 3.42-3.51 (8H, m), 4.12 (2H, s), 6.75 (2H, d, J = 8.5 Hz) and 7.18 (2H, d, J = 8.5 Hz).

Piperazine-1-carbothioic acid S-[4-(3-nitrobenzyl)oxy]benzyl ester: A mixture [(4-tert-butyl-dimethylsilyloxy)benzylsulfanylcarbonyl]-piperazine-4-carboxylic acid tert-butyl ester (0.05 g), 3-nitrobenzyl bromide (0.028 g), cesium fluoride (0.033 g) and DMF (1 mL) was shaken for 48 h then partitioned between water (2 mL) and dichloromethane (2 mL). The separated organic layer was concentrated in vacuo then suspended in trifluoroacetic acid – dichloromethane (1:1, 1 mL) and shaken for 18 h. The mixture was concentrated in
15 vacuo and purified by preparative HPLC [C18, 10 mM aqueous NH₄OAc solution: MeOH] to afford the product (0.011 g, 25%). HPLC: [Xterra, 2.0 mL/min; methanol-10 mM aqueous ammonium acetate solution (50:50) to (80:20) over 5 min then (80:20)] 98% (5.1 min); MS (ISP): 387 MH⁺.

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Example 52

Piperazine-1-carboxylic acid 3-(2-phenylethoxy)-benzyl ester hydrochloride

Piperazine-1,4-dicarboxylic acid (3-tert-butyldimethylsilyloxy)benzyl ester tert-butyl ester: A solution of 3-tert-butyldimethylsilyloxybenzyl alcohol (Tetrahedron Lett. 26, 681 (1985)) (5.0 g), triethylamine (8.7 mL), pyridine (1.65 mL) and 4-chlorocarbonyl-
25 piperazine-1-carboxylic acid tert-butyl ester (5.1 g) in dichloromethane (200 mL) was stirred for 96 h. 4-Dimethylaminopyridine (0.20 g) was added and the mixture was heated to reflux for 4 h. The mixture was cooled to room temperature, washed with water (100 mL), brine (100 mL), dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography [SiO₂; dichloromethane, isopropyl ether:
30 (100:0) to (80:20)] to give the product as a yellow oil (3.8 g, 41%). ¹H-NMR (400 MHz, CDCl₃): 0.19 (6H, s), 0.98 (9H, s), 1.46 (9H, s), 3.36-3.43 (4H, m), 3.44-3.50 (4H, m), 5.08

(2H, s), 6.78 (1H, dd, $J = 2.5, 8$ Hz), 6.82 (1H, t, $J = 2$ Hz), 6.92 (1H, d, $J = 8$ Hz) and 7.20 (1H, t, $J = 8$ Hz).

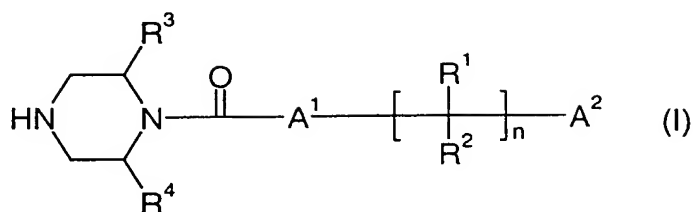
Piperazine-1,4-dicarboxylic acid (3-hydroxy)benzyl ester tert-butyl ester: To a stirred
5 solution of piperazine-1,4-dicarboxylic acid (3-tert-butyldimethylsilyloxy)benzyl ester
tert-butyl ester (0.50 g, 1.1 mmol) in anhydrous THF (10 mL) at 0°C were added
sequentially a solution of tetrabutylammonium fluoride in THF (1 M, 4.4 mL, 4.4 mmol)
and glacial acetic acid (0.76 mL, 13.3 mmol). The mixture was stirred for 1 h then poured
into water (40 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic
10 extracts were washed with water (3 x 25 mL), saturated aqueous sodium
hydrogencarbonate solution (25 mL) and brine (25 mL) then dried over magnesium
sulfate and concentrated in vacuo to give the product as a colourless oil which solidified on
standing (0.38 g, 100%). ¹H-NMR (400 MHz, CDCl₃): 1.46 (9H, s), 3.38-3.44 (4H, m),
3.45-3.50 (4H, m), 5.09 (2H, s), 6.79 (1H, dd, $J = 2.5, 8$ Hz), 6.83 (1H, m, OH), 6.90 (1H, d, J
15 = 8 Hz), 7.22 (1H, t, $J = 8$ Hz) and 7.26 (1H, s). HPLC [Xterra, 2.0 mL/min; methanol-10
mM aqueous ammonium acetate solution (50:50) to (80:20) over 5 min then (80:20)]
100% (3.59 min).

Piperazine-1,4-dicarboxylic acid 3-(2-phenylethoxy)benzyl ester tert-butyl ester : To a
20 solution of piperazine-1,4-dicarboxylic acid (3-hydroxy)benzyl ester tert-butyl ester (0.16
g, 0.48 mmol) in acetone (5 mL) at 0°C was added potassium carbonate (0.072 g, 0.52
mmol) and the reaction mixture was stirred at 0°C for 30 min. (2-Bromoethyl)-benzene
(0.097 g, 0.52 mmol) was added and the reaction mixture was allowed to warm to room
temperature and then heated under reflux for 24 h. After cooling, the reaction mixture was
25 concentrated in vacuo and the residue was partitioned between water (20 mL) and ethyl
acetate (20 mL). The organic phase was separated, washed with saturated brine (25 mL),
dried (MgSO₄) and concentrated in vacuo to give an oil which was purified by column
chromatography [SiO₂; heptane-ethyl acetate (3 : 1)] to yield the title compound (0.10 g,
48%) as a colourless oil. ¹H-NMR (400 MHz, CDCl₃): 1.46 (9H, s), 3.10 (2H, t, $J = 7.0$
30 Hz), 3.40 (4H, m), 3.46 (4H, m), 4.18 (2H, t, $J = 7.0$ Hz), 5.09 (2H, s), 6.84 (1H, m), 6.88
(1H, m), 6.91 (1H, m) and 7.22 – 7.34 (6H, m).

Piperazine-1-carboxylic acid 3-(2-phenylethoxy)-benzyl ester hydrochloride: To a solution of piperazine-1,4-dicarboxylic acid 3-(2-phenylethoxy)benzyl ester tert-butyl ester (0.10 g, 0.23 mmol) in methanol (2 mL) and ether (2 mL) was added 4M HCl in 1,4-dioxane (2.3 mL, 9.2 mmol) and the solution was left to stand with occasional swirling at room
5 temperature for 3 h. The solution was concentrated in vacuo and the residue was triturated with ether to yield the title compound (0.08 g, 93%) as a white solid. ¹H-NMR (400 MHz, *d*₆-DMSO): 3.03 (2H, t, *J* = 6.8 Hz), 3.08 (4H, m), 3.61 (4H, m), 4.19 (2H, t, *J* = 7.0 Hz), 5.06 (2H, s), 6.88 – 6.94 (3H, m), 7.20 – 7.33 (6H, m) and 9.19 (2H, br s).

CLAIMS

1. A compound of formula (I):



wherein

R¹ and R² are independently selected from hydrogen, alkyl, cycloalkyl, aryl and aralkyl or R¹ and R² together with the carbon atom to which they are attached form a 3- to 8-membered carbocyclic ring which is optionally substituted with alkyl;

10

R³ and R⁴ are independently selected from hydrogen, alkyl, cycloalkyl, aryl and aralkyl;

A¹ is oxygen or sulfur, wherein in case A¹ is oxygen and A² is unsubstituted phenyl one of R¹, R², R³ and R⁴ is not hydrogen;

15

A² is aryl, heteroaryl or cycloalkyl each optionally substituted with one or more substituents independently selected from halogen, alkyl, cycloalkyl, aryl, aralkyl, alkoxy, aralkoxy, aryloxy, hydroxy, cyano, nitro, amino, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heteroaryloxycarbonyl and carbamoyl, wherein alkyl, cycloalkyl, aryl, aralkyl, alkoxy, aralkoxy, aryloxy, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl and heteroaryloxycarbonyl are optionally substituted with one to three substituents independently selected from alkyl, alkoxy, halogen and nitro,

20

or two substituents of aryl, heteroaryl or cycloalkyl form together with the carbon atoms to which they are attached a 5- to 7-membered carbocyclic ring which is optionally substituted with alkyl, alkoxy or halogen;

n is 1 or 2

5 and their pharmaceutically usable salts, solvates and esters; wherein 2-methyl-1-piperazinecarboxylic acid (4-nitrophenyl)methyl ester and 1-piperazinecarboxylic acid (4-(trifluoromethyl)phenyl)methyl ester are excluded.

- 10 2. A compound according to claim 1, wherein R^3 and R^4 are independently selected from hydrogen and alkyl.
3. A compound according to claim 1 or 2, wherein R^3 and R^4 are both hydrogen or wherein R^3 and R^4 are both methyl.
4. A compound according to any one of claims 1 to 3, wherein A^1 is oxygen.
5. A compound according to any one of claims 1 to 4, wherein A^1 is sulfur.
- 15 6. A compound according to any one of claims 1 to 5, wherein R^1 and R^2 are independently selected from hydrogen, alkyl and aryl.
- 20 7. A compound according to any one of claims 1 to 6, wherein A^2 is phenyl, naphthalenyl, cycloalkyl, pyridyl, thienyl, pyrazinyl or furyl, each optionally substituted with one or more substituents independently selected from halogen, alkyl, cycloalkyl, aryl, aralkyl, alkoxy, aralkoxy, aryloxy, hydroxy, cyano, nitro, amino, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heteroaryloxycarbonyl and carbamoyl, wherein alkyl, cycloalkyl, aryl, aralkyl, alkoxy, aralkoxy, aryloxy, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl and heteroaryloxycarbonyl are optionally substituted with one to three substituents independently selected from alkyl, alkoxy, halogen and nitro, or two substituents of aryl, heteroaryl or cycloalkyl form together with the carbon atoms to which they are attached a 5- to 7-membered carbocyclic ring which is optionally substituted with alkyl, alkoxy or halogen.
- 25

8. A compound according to any one of claims 1 to 7, wherein A² is phenyl, naphthalenyl, cyclohexyl, pyridyl or thienyl each optionally substituted with one or more substituents independently selected from halogen, alkyl, cycloalkyl, aryl, aralkyl, alkoxy, aralkoxy, aryloxy, hydroxy, cyano, nitro, amino, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, heteroaryloxycarbonyl and carbamoyl, wherein alkyl, cycloalkyl, aryl, aralkyl, alkoxy, aralkoxy, aryloxy, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl and heteroaryloxycarbonyl are optionally substituted with one to three substituents independently selected from alkyl, alkoxy, halogen and nitro.
9. A compound according to any one of claims 1 to 8, wherein A² is phenyl, naphthalenyl, cyclohexyl, pyridyl or thienyl each optionally substituted with one or more substituents independently selected from halogen, alkyl, aryl, alkoxy, aralkoxy, cyano, nitro, alkoxycarbonyl, wherein alkyl, alkoxy, aralkoxy and alkoxycarbonyl are optionally substituted with one to three substituents independently selected from halogen and nitro.
10. A compound according to any one of claims 1 to 9, wherein A² is phenyl optionally substituted with one to five substituents independently selected from halogen, alkyl, aryl, alkoxy, aralkoxy, cyano, nitro, alkoxycarbonyl, wherein alkyl, alkoxy and aralkoxy are optionally substituted with one to three substituents independently selected from halogen and nitro.
11. A compound according to any one of claims 1 to 10, wherein n is 1.
12. A compound according to any one of claims 1 to 11 selected from:
- piperazine-1-carboxylic acid 4-trifluoromethoxy-benzyl ester;
- piperazine-1-carboxylic acid 2-chloro-benzyl ester;
- piperazine-1-carboxylic acid 4-difluoromethoxy-benzyl ester;
- piperazine-1-carboxylic acid 2-fluoro-benzyl ester;
- cis-2,6-dimethyl-piperazine-1-carboxylic acid 4-chloro-benzyl ester;
- piperazine-1-carbothioic acid S-(4-benzyloxy-benzyl) ester;
- piperazine-1-carbothioic acid S-(2,4-difluoro-benzyl) ester;

piperazine-1-carbothioic acid S-(4-methoxy-benzyl) ester;

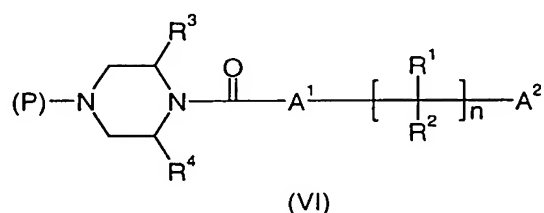
piperazine-1-carbothioic acid S-[4-(4-fluoro-benzyloxy)-benzyl] ester;

piperazine-1-carboxylic acid 4-(4-fluoro-benzyloxy)-benzyl ester;

cis-2,6-dimethylpiperazine-1-carboxylic acid 2-(2-thienyl)ethyl ester and

5 cis-2,6-dimethylpiperazine-1-carboxylic acid 2-fluoro-benzyl ester.

13. A process for the preparation of a compound according to any one of claims 1 to 12 comprising the deprotection of a compound according to formula



10 wherein R^1 to R^4 , A^1 , A^2 and n are defined as in claim 1 and (P) is a nitrogen protecting group.

14. A compound in accordance with any one of claims 1 to 12 for use as therapeutically active substances.
15. A compound in accordance with any one of claims 1 to 12 for the production of medicaments for the prophylaxis and therapy of illnesses which are caused by disorders associated with the 5-HT₂ receptor.
16. A pharmaceutical composition comprising a compound in accordance with any one of claims 1 to 12 and a therapeutically inert carrier.
17. The use of a compound in accordance with any one of claims 1 to 12 for the production of medicaments for the treatment and prophylaxis of eating disorders and obesity.
- 20 18. The use of a compound in accordance with any one of claims 1 to 12 for the production of medicaments for the treatment and prophylaxis of disorders of the central nervous system, cardiovascular disorders, gastrointestinal disorders, diabetes insipidus and sleep apnoea.

19. The use according to claim 18, wherein the disorders of the central nervous system are selected from depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, bulimia, anorexia nervosa, premenstrual tension, trauma, stroke, neurodegenerative diseases, encephalitis and meningitis.
20. A compound in accordance with any one of claims 1 to 12, when manufactured according to claim 13.
21. A method for the treatment and prophylaxis of disorders of the central nervous system, cardiovascular disorders, gastrointestinal disorders, diabetes insipidus, and sleep apnoea, which method comprises administering an effective amount of a compound in accordance with any one of claims 1 to 12.
22. A method according to claim 21, wherein the disorders of the central nervous system are selected from depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, bulimia, anorexia nervosa, premenstrual tension, trauma, stroke, neurodegenerative diseases, encephalitis and meningitis.
23. A method for the treatment and prophylaxis of eating disorders and obesity, which method comprises administering an effective amount of a compound in accordance with any one of claims 1 to 12.
24. A method of treatment of obesity in a human in need of such treatment which comprises administration to the human a therapeutically effective amount of a

compound according to any one of claims 1 to 12 and a therapeutically effective amount of a lipase inhibitor.

25. The method according to claim 24, wherein the lipase inhibitor is orlistat.

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26. The method according to claims 24 and 25 for the simultaneous, separate or sequential administration.

27. The use of a compound according to any one of claims 1 to 12 in the manufacture of a medicament for the treatment and prevention of obesity in a patient who is also receiving treatment with a lipase inhibitor.

28. The use according to claim 27, wherein the lipase inhibitor is orlistat.

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29. The pharmaceutical composition according to claim 16 comprising further a therapeutically effective amount of a lipase inhibitor.

30. The pharmaceutical composition according to claim 29, wherein the lipase inhibitor is orlistat.

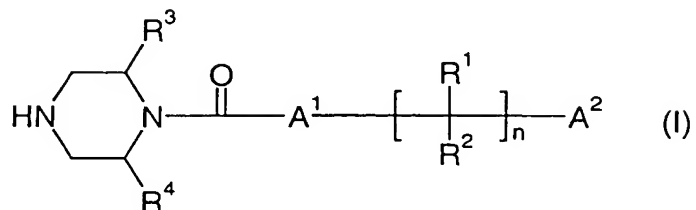
31. The invention as hereinbefore described.

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ABSTRACT

The present invention refers to chemical compounds of formula (I)

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as well as pharmaceutically usable salts, solvates and esters thereof, wherein R¹ to R⁴, A¹, A² and n have the significance given in claim 1. They can be used in the form of

10 pharmaceutical preparations for the treatment or prevention of disorders of the central nervous system, cardiovascular disorders, gastrointestinal disorders, diabetes insipidus, obesity and sleep apnoea.
